THE American Journal OF Gastroenterology

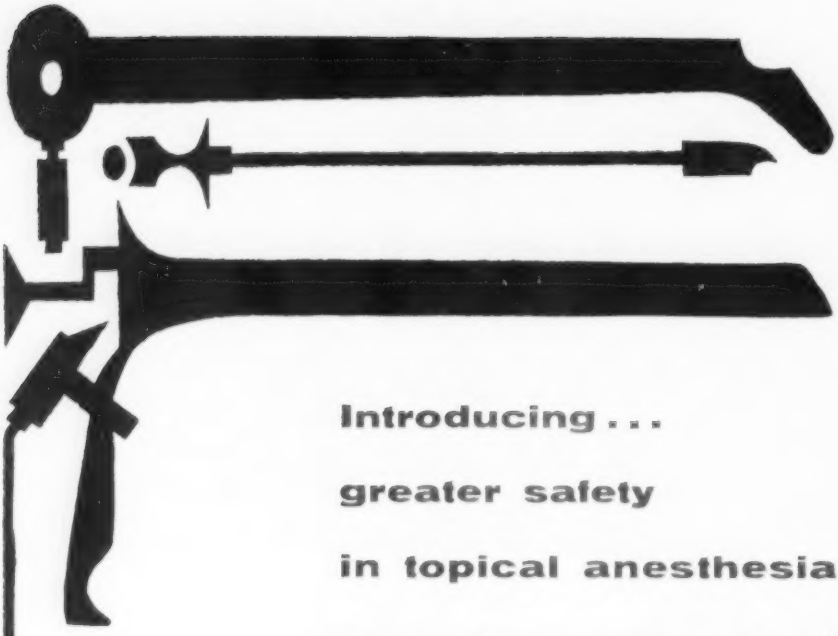
VOL. 23, NO. 4 APRIL, 1955

PANEL DISCUSSION ON AMEBIASIS:
Therapeutic Problems
Research Approach to Clinical Problems
Laboratory Approach
Factors Related to the Pathogenicity of Endameba Histolytica
Clinical Aspects
Clinical Considerations of Amebiasis
Parasitological Considerations
Serological Considerations
Experience in the Treatment of Amebiasis

The Treatment of Celiac Disease with the Specific Carbohydrate Diet

Second Annual Convention
Chicago, Ill.
24, 25, 26 October 1955

Official Publication
AMERICAN COLLEGE OF GASTROENTEROLOGY



Introducing . . .

greater safety

in topical anesthesia

Pyribenzamine®

Anesthetic Solution and Jelly

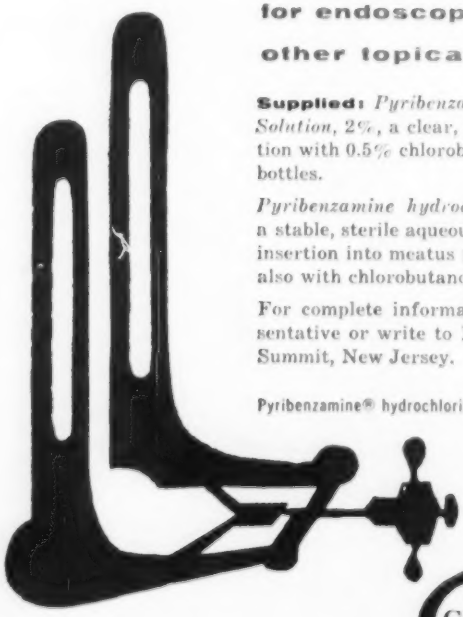
for endoscopic procedures and other topical anesthetic uses

Supplied: *Pyribenzamine hydrochloride Anesthetic Solution*, 2%, a clear, nonviscous, stable, sterile solution with 0.5% chlorobutanol as preservative; in 1-oz. bottles.

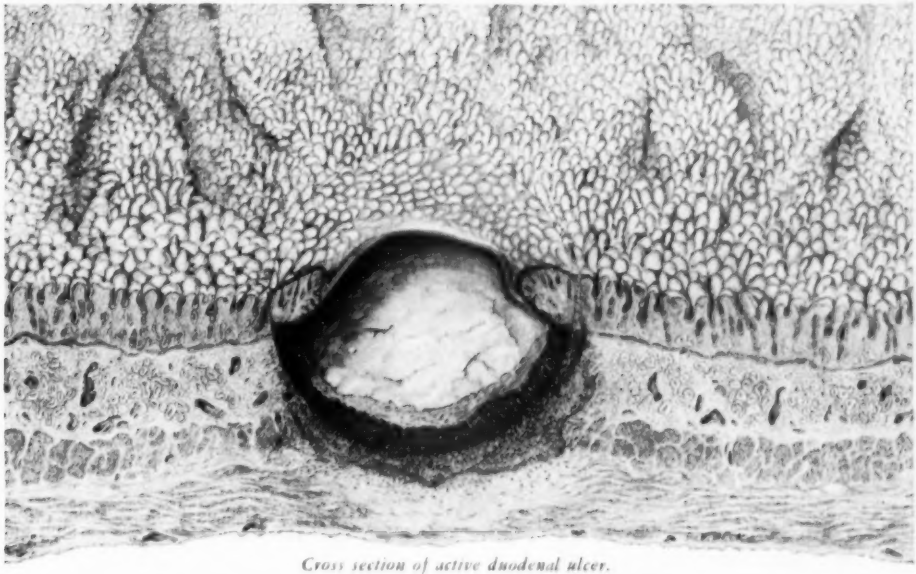
Pyribenzamine hydrochloride Anesthetic Jelly, 2%, a stable, sterile aqueous jelly with applicator tip (for insertion into meatus for intra-urethral instillation), also with chlorobutanol; in 1-oz. tubes.

For complete information, consult your CIBA representative or write to Medical Service Division, CIBA, Summit, New Jersey.

Pyribenzamine® hydrochloride (tripelennamine hydrochloride CIBA)



C I B A Summit, N. J.



Cross section of active duodenal ulcer.

Dramatic Remission of Ulcer Pain

Pain of ulcer is associated with hypermotility; the pain is relieved when abnormal motility is controlled by Pro-Banthine.

"In studying[1] the mechanism of ulcer pain, it is obvious that there are at least two factors which must be considered: namely, hydrochloric acid and motility.

". . . our studies indicate that ulcer pain in the uncomplicated case is invariably associated with abnormal motility. . . .

"Prompt relief of ulcer pain by ganglionic blocking agents . . . coincided exactly with cessation of abnormal motility and relaxation of the stomach."

Pro-Banthine Bromide (β-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is a new, improved, well tolerated anticholinergic agent which consistently reduces hypermotility of the stomach and intestinal tract. In peptic ulcer therapy[2] Pro-Banthine has brought about dramatic remissions, based on roentgenologic evidence. Concurrently there is a reduction of pain, or in many instances, the pain and discomfort disappear early in the program of therapy.

One of the typical cases cited by the authors[2] is that of a male patient who refused surgery despite the presence of a huge crater in the duodenal bulb.

"This ulcer crater was unusually large, yet on 30 mg. doses of Pro-Banthine [q.i.d.] his symptoms were relieved in 48 hours and a most dramatic diminution in the size of the crater was evident within 12 days."

Pro-Banthine is proving equally effective in the relief of hypermotility of the large and small bowel, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm. G. D. Searle & Co., Research in the Service of Medicine.

---

1. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

SEARLE

Noludar / 'Roche'

a new, mild sedative-hypnotic

with **onset of action within ½ hour—average duration of 6 to 7 hours**
low toxicity

without **barbiturate "hangover"**
drowsiness from sedative doses

Clinical studies in over 3000 patients have confirmed the usefulness of Noludar in the relief of nervous insomnia and daytime tension.

Tablets: 200 mg (bottles of 100 and 1000).
50 mg (bottles of 100 and 1000).

Elixir: 50 mg per teaspoonful—4 cc
(bottles of 16 oz and 1 gal).

Hoffmann-La Roche Inc.
Roche Park · Nutley 10 · New Jersey

Noludar™—brand of methyprylon (3,3-diethyl-5-methyl-2, 4-piperidinedione).

not a barbiturate

VOL. 23, NO. 4 APRIL, 1955

THE American Journal OF Gastroenterology

(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

The Pioneer Journal of Gastroenterology, Proctology and Allied Subjects in the United States and Canada

contents:

Editorial Board and General Information 288

PANEL DISCUSSION ON AMEBIASIS:

Therapeutic Problems in Amebiasis as Viewed by a Clinician
HENRY A. MONAT, A.B., M.D., F.A.C.P., F.A.C.G. 295

The Research Approach to Clinical Problems in Amebiasis
NORMAN B. MCCULLOUGH, Ph.D., M.D. 299

The Laboratory Approach to Problems in Amebiasis
WILLARD H. WRIGHT, Ph.D. 303

Factors Related to the Pathogenicity of *Endameba Histolytica*
CHARLES W. REES, B.S., M.A., Ph.D. 307

Clinical Aspects of Amebiasis with Observations on Variations in Tropical and Temperate Zones.....CLARENCE A. IMBODEN, JR., M.D. and HENRY K. BEYE, M.D. 311

Clinical Considerations of Amebiasis.....LUTHER L. TERRY, M.D. 325

Parasitological Considerations Relative to the Diagnosis of Amebiasis
JOHN E. TOBIE, Ph.D. 329

Serological Considerations Relative to the Diagnosis of Amebiasis
JOHN BOZICEVICH, M.S. 332

Experience in the Treatment of Amebiasis at the USPHS Hospital, Baltimore.....LUTHER L. TERRY, M.D. and CHARLES G. SPICKNALL, M.D. 335

The Treatment of Celiac Disease with the Specific Carbohydrate Diet
SIDNEY V. HAAS, M.D. and MERRILL P. HAAS, M.D. 344

Report of Research Committee 361

Editorial:

Urinary Uropepsin as an Index in Diagnosis of Benign and Malignant States of the Gastrointestinal Tract..SAMUEL WEISS, M.D., F.A.C.G. 363

Ames Awards Contest 365

News Notes 366

President's Message 368

Abstracts for Gastroenterologists 369

Book Reviews for Gastroenterologists 378

Owned and published monthly by the American College of Gastroenterology, Inc. Business Office: 33 West 60th St., New York 23, N. Y. Editorial Office: 146 Central Park West, New York 23, N. Y. Copyright, 1955, by the American College of Gastroenterology, Inc. Subscription rate, U. S. and possessions: One year $8.00, two years $14.00 (foreign $10.00, $18.00). Single copy: $.75. Reentered as second class matter at the Post Office at New York, N. Y., under the act of March 3, 1879.

Index to Advertisers

Ames Co., Inc. 294
Astra Pharmaceutical Products, Inc. 387
Burton Parsons & Co. 3rd cover
Ciba Pharmaceutical Products, Inc. 2nd cover
Endo Products, Inc. 290
Hoffmann-La Roche, Inc. 286
Horlicks Corp. 364
Lakeside Laboratories, Inc. 292, 293
Massengill, The S. E., Co. 386
Pfizer Laboratories 384, 385
Rorer, William H., Inc. 384, 388
Schering Corp. 381
Searle, G. D., & Co. 285
Upjohn Co. 291
U. S. Treasury 382
Warner-Chilcott Laboratories 4th cover
Winthrop-Stearns, Inc. 289

OFFICIAL PUBLICATION

of the

AMERICAN COLLEGE OF GASTROENTEROLOGY

33 West 60th Street, New York 23, N. Y.

Editorial Office, 146 Central Park West, New York 23, N. Y.

SAMUEL WEISS, *Editor-in-Chief*

EDITORIAL BOARD

JAMES A. FERGUSON
MILTON J. MATZNER
J. R. VAN DYNE
MICHAEL W. SHUTKIN

EDITORIAL COUNCIL

ANTHONY BASSLER
F. W. BANCROFT
RICHARD BAUER
BENJAMIN M. BERNSTEIN
THEODOR BLUM
DONOVAN C. BROWNE
JOSE OVEIDO BUSTOS
LOUIS H. CLERF
FRANK A. CUMMINGS
FELIX CUNHA
HARRY M. EBERHARD
RUDOLF R. EHRMANN
LYNN A. FERGUSON
CHEVALIER L. JACKSON
WILLIAM C. JACOBSON
I. R. JANKELSON
SIGURD W. JOHNSEN
ELIHU KATZ
ARTHUR A. KIRCHNER
WILLIAM W. LERMANN
FRANZ J. LUST
CHARLES W. MCCLURE
LESTER M. MORRISON
GEORGE G. ORNSTEIN
GEORGE T. PACK
GEORGE E. PFAHLER
MARTIN E. REHFUSS
A. X. ROSSIEN
DAVID J. SANDWEISS
JOSEPH SCHROFF
MARKS S. SHAINE
I. SNAPPER
J. EARL THOMAS
MAX THOREK
C. J. TIEMARSH
GABRIEL TUCKER
ROY UPHAM
F. H. VOSS
MICHAEL WEINGARTEN
LESTER R. WHITAKER
FRANK C. YEOMANS

Publication Office, 33 West 60th Street, New York 23, N. Y.

DANIEL WEISS, *Managing Editor*

STEVEN K. HERLITZ, *Advertising Manager*

Contributions: Articles are accepted for publication on condition that they are contributed solely to THE AMERICAN JOURNAL OF GASTROENTEROLOGY. Manuscripts should be typewritten double-spaced and submitted in two copies. Footnotes and bibliographies should conform to the style recommended by the American Medical Association, illustrations and diagrams should carry suitable lettering and explanations, be mounted on separate pages and have the name of the author on each page. Four illustrations per article are allowed without cost to the author.

Reviews: THE AMERICAN JOURNAL OF GASTROENTEROLOGY will review monographs and books dealing with gastroenterology or allied subjects. It may be impossible to review all material sent. However, an acknowledgement will be made in the Department of Reviews.

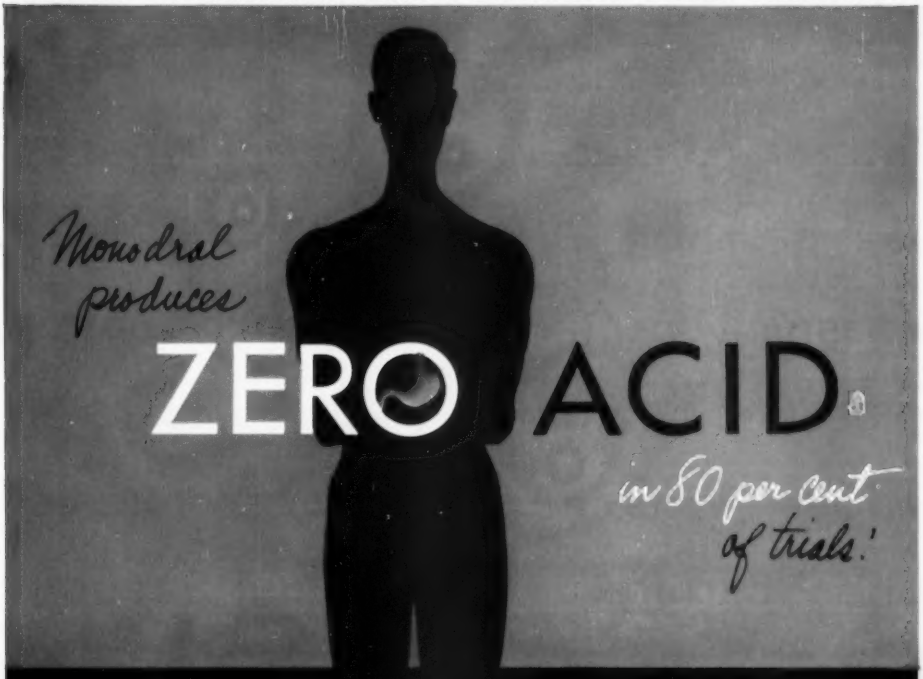
The editors and publishers are not responsible for individual opinions expressed by their contributors, nor for those given under current literature.

Reprints: A price list and order blank for reprints will be sent to each contributor before the journal is issued.

Subscription price: U.S. and possessions: one year, $8.00, two years, $14.00. Elsewhere, $10.00, $18.00. Single copy $.75. Members of the American College of Gastroenterology receive the JOURNAL as part of their membership.

Change of Address: Notify publishers promptly of change of address. Notices should give both old and new addresses.

NOW – ACHLORHYDRIA FOR MOST ULCER PATIENTS



Complete suppression of HCl production was attained in 38 of 47 tests conducted among duodenal ulcer patients. Zero acid plus the powerful antimotility action of Monodral provides faster pain relief – faster, more certain healing.

Monodral®

bromide CAPLETS, 5 mg. ELIXIR, 2.5 mg./cc.

and now **MONODRAL WITH MEBARAL**

Sedation for ulcer patients—without drowsiness.

Mebaral,® a barbituric acid derivative, is sedative and antispasmodic. It has a wide margin between sedative and hypnotic dose. Mebaral calms without impairing efficiency, relaxes without drowsiness. Ideal sedation for ulcer patients in high gear who "can't slow down." Monodral 5 mg. with Mebaral 32 mg. (½ grain) tablets.

1. MCKENNA, R.D., ROYAL VICTORIA HOSPITAL, MONTREAL, CANADA - PERSONAL COMMUNICATION.

Winthrop-Stearns INC.

New York 18, N. Y. • Windsor, Ont.

for the "squeeze" of g.i. spasm...

when indigestion, pain, heartburn, belching, or nausea is due to g.i. spasm, MESOPIN-PB* provides the selective spasmolytic effectiveness of homatropine methylbromide (1/30 as toxic as atropine) plus the sustained sedation of phenobarbital . . . with virtual freedom from undesirable atropine effects

MESOPIN-PB

Trademark

Yellow tablets and elixir containing 2.5 mg. MESOPIN* (homatropine methylbromide) and 15 mg. phenobarbital per tablet or teaspoonful. Also as MESOPIN-PB double strength in green tablets containing 5 mg. MESOPIN and 15 mg. phenobarbital. MESOPIN (without phenobarbital) is available as 2.5 mg. white tablets and green elixir, and MESOPIN double strength 5 mg. peach tablets.

Endo®

Literature? write

ENDO PRODUCTS, Inc.
Richmond Hill 18, New York

*TRADEMARK OF ENDO PRODUCTS INC.

Upjohn

preoperative bowel preparation within 24 hours:

Mycifradin *tablets*

Trademark for the Upjohn brand of neomycin

Each tablet contains 0.5 Gm. neomycin sulfate (equivalent to 0.35 Gm. neomycin base). In bottles of 20 tablets.

Also available:

Mycifradin Sulfate Powder (topical) in vials of 0.5 Gm. and 5 Gm.

Mycifradin Sulfate (intramuscular) in vials of 0.5 Gm.

THE UPJOHN COMPANY, KALAMAZOO, MICHIGAN

NOW PIPERIDOL ACTION

for peptic ulcer pain ⌐ spasm

cholinolytic

PIPTAL®

RELIEF DAY AND NIGHT

without urinary retention or

constipation

NORMALIZES GASTRIC MOTILITY AND SECRETION

Closely related to the visceral eutonic DACTIL®, PIPTAL curbs gastric hypermotility and duodenal spasm without significantly altering normal tonus or motility. A postganglionic parasympathetic inhibitor, cholinolytic PIPTAL normalizes gastric secretion, favors ulcer healing without undue interference with digestion.

WITHOUT URINARY RETENTION OR CONSTIPATION

Unlike compounds of other derivation, the effect of PIPTAL, latest LAKESIDE piperidol, is negligible on bladder and distal colon. Mydriasis, dryness of the mouth and tachycardia occur infrequently and are usually mild and transient. Side effects necessitating withdrawal of PIPTAL have not been observed.

cholinolytic

PIPTAL

Use the Patient Report Form accompanying mailed samples and see it work in your practice.

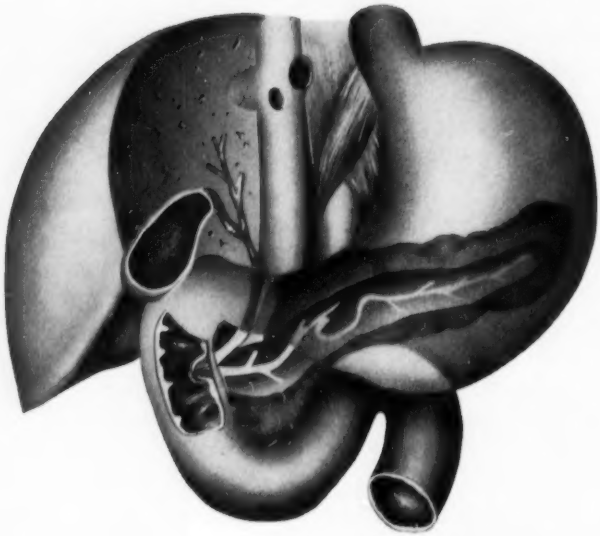
For relief day and night: One tablet T.I.D. and one or two H. S. Each tablet contains 5 mg. of PIPTAL, the *only* brand of N-ethyl-3-piperidyl -benzilate methobromide.

Lakeside Laboratories Inc. PIONEERS IN PIPERIDOLS Milwaukee 1, Wisconsin

79455

patients with liver and gallbladder disorders

*benefit from biliary flush**



more successful medical

and

pre- and postoperative management

true *hydro*choleresis plus reliable spasmolysis corrects biliary stasis, improves liver function, relieves functional G. I. distress...

flushes liver stones into surgical zone, helps dislodge residual calculi, tends to prevent postcholecystectomy syndrome.

DECHOLIN® with Belladonna

(dehydrocholic acid and belladonna, *Ames*)

Each tablet of *Decholin*/Belladonna contains *Decholin* 3¾ gr., and extract of belladonna ⅙ gr. (equivalent to tincture of belladonna, 7 minims).

* Complete information on Three-Day Biliary Flush available from your Ames Professional Service Representative—or write to Medical Service Department.

AMES
COMPANY, INC · ELKHART, INDIANA

Ames Co. of Canada, Ltd., Toronto

63458

THE American Journal OF Gastroenterology

A monthly journal of Gastroenterology, Proctology and Allied Subjects
(FORMERLY THE REVIEW OF GASTROENTEROLOGY)

VOLUME 23 APRIL, 1955 NUMBER 4

PANEL DISCUSSION ON AMEBIASIS

THERAPEUTIC PROBLEMS IN AMEBIASIS AS VIEWED BY A CLINICIAN*

HENRY A. MONAT, A.B., M.D., F.A.C.P., F.A.C.G.
Washington, D. C.

From the enthusiastic reports of different "sure cures" in medical literature, one feels certain to realize how ephemeral the treatment of amebiasis is at present. Initial response or failure of this disease to various remedies is *not* a criterion of its ultimate eradication. One must consider the following points before launching treatment:

1. Does the patient have amebiasis? Are the laboratory studies performed by a competent technician who actually is trained to identify cysts and trophozites? Were a sufficient number of stools taken? Were they taken on alternate days, inasmuch as cysts may show up one day and not the next day?

2. How long has the patient had the symptoms of amebiasis? Under this heading will come questions whether there was an outbreak of amebiasis in the locality where he was living; whether he lived in places where amebiasis is endemic; whether he lived in a household in which a member harbored amebic dysentery.

3. The physical condition of the patient. Is he anemic? Did he have concommitant gastrointestinal symptoms preceding or following this so-called amebiasis attack? What do the gastrointestinal and gallbladder x-ray films show? What does the x-ray of the chest reveal, especially in reference to the raised right dome of the diaphragm? What does the gastric analysis reveal?

The successful treatment of this disease is predicated partly upon the above outlined rules and upon understanding that ameba cannot live without symbiosis with other bacteria. And, (sic!) "other bacteria" are not always responsive to

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

one type of antibiotic! This phenomenon is the answer why certain individuals are cured with the help of one antibiotic and others do not respond at all.

How do we handle these various clinical situations? Let us take first problematic patient A. He has an uncontrolled plain or sanguinous diarrhea. Stools reveal trophozites or cysts of *endameba histolytica*. This patient is placed on 2 gm. of Achromycin daily for 10 days and on Aralen-Milibis tablets one q.i.d. at the same time for 14 days. His diet is adjusted according to the involvement of his digestive tract. Ordinarily he is given a bland, high protein and adequate fluid diet. Six weeks later his stools are studied again. If no cysts are found and he is clear symptomatically, the patient is told to return in six months for another stool study and a blood complement fixation test for amebiasis. If, then, these tests are negative, the patient is considered cured.

Patient B tells of having had diarrhea on and off for several months or years. He was diagnosed before as having either mucous colitis, irritable colon, or being psychosomatic. Our stool studies are positive for cysts of ameba histolyitica; his complement fixation test is negative. Here we are dealing with colonic amebiasis in its mild chronic form and we treat him as we do Patient A, with the exception that stools are again examined one month after treatment. If cysts are found at this time a second course of therapy is instituted. This consists of one c.c. of combiotic (penicillin, streptomycin) daily for six days with one tablet of Aralen twice daily for 14-21 days. Six weeks later stools are again studied and if still positive, Fumidil (Abbott) 15 q.i.d. is given with one tablet b.i.d. of Aralen for 14 days. This type of therapeutic perseverance assures quite a large degree of success in eradication of ameba. Personally, I have not seen recurrence after two courses of the outlined treatment provided, of course, that the complement fixation test was negative.

Patient C may tell that he lived in the tropics, that he, like everyone else in the tropics, occasionally had diarrhea; notices intolerance to certain foods or especially coffee, which give him a loose movement. He feels mainly an indescribable lassitude; he may state that it is hard for him to concentrate mentally and he complains of an uncomfortable feeling in the liver area, especially on physical exertion. Stool studies, as many as 10-20, may or may not reveal the cysts of ameba. The complement fixation test for amebiasis is positive. This type of patient receives one c.c. of combiotic for six days, followed by 2 gm. in divided doses of Achromycin for 10 days. At the same time, Aralen-Milibis tablets are taken one q.i.d. for 16 days.

The patient with this supposedly hepatic involvement is placed on a low fat, high protein, high carbohydrate diet and given 100 mg. of Thiamine and 30 micrograms of Rubramin daily hypodermically for 30 days. Six weeks later the complement fixation test is repeated and if positive, the reduction in titre is ascertained. If the titre is lowered from the original one or if the CFT is nega-

tive, the patient is considered cured. The CFT is repeated six months later and in the majority of these chronic cases, becomes negative.

This point is worthwhile to remember, that the CFT after treatment may become negative after a certain period of time. A strong CFT is a presumption that ameba is still in the body; and, treatment repeated if the CFT of the same titre as previously persists. Liver abscess should be then suspected and a liver biopsy is in order.

The CFT, in spite of being greatly maligned, in the hands of an intelligent therapeutist is an invaluable aid in determining the diagnosis, the type of treatment to undertake and the prognosis. A positive CFT to me means definitely that the patient harbors amebiasis! Without positive stool findings it may mean that patient C has an extraintestinal amebiasis.

As a final admonition to my colleagues who will treat amebiasis, let me restate that it requires painstaking attention to physiological details and a great degree of optimism in the face of discouraging response.

Summary

The problems and pitfalls of the treatment of amebiasis were analyzed. The crux of the treatment was discussed; whereas that ameba cannot live unless in symbiosis with other bacteria; therefore, the failure of one antibiotic to cure certain type of amebiasis. The treatment of extraintestinal and intestinal amebiasis was outlined and the value of complement fixation test in determination of its cure was explained.

BIBLIOGRAPHY

Armitage, F. L.: Amebic Abscess of Brain: With Notes of Case Following Amebic Abscess of Liver. J. Trop. Med. & Hyg. **22**:69, 1919.

Armstrong, T. G., Wilmot, A. J. and Elsdon-Dew, R.: Aureomycin and Amebic Dysentery. Lancet **2**:10 (July 1), 1950.

Banker, D. D.: Amebic Abscess of the Liver. Indian Physician **6**:254, 1947. Abstract in Trop. Dis. Bull. **45**:338, 1948.

Brown, E., Burson, E. N. and Ransmeier, J. C.: Aureomycin and Terramycin in Treatment of Amebic Colitis. Am. J. Med. **11**:620, (Nov.), 1951.

Conan, N. J., Jr.: Chloroquine in Amebiasis. Am. J. Trop. Med. **28**:107 (Jan.), 1948.

Craig, C. F.: Amebiasis and Complement Fixation Test. U. S. Armed Forces M. J. **1**:1337, (Nov.), 1950.

D'Antoni, J. S.: Concepts and Misconceptions in Amebiasis. Am. J. Trop. Med. & Hyg., **1**:146, (Jan.), 1952.

DeSilva, P. C. C.: Amebiasis in Infancy. Brit. M. J. **2**:1208, (Nov. 26), 1949.

Hargreaves, W. H.: Chronic Amebic Dysentery: A New Approach to Treatment. Lancet **2**:68, 1945.

Hoekenga, M. T.: The Prophylaxis of Malaria and Amebiasis with Milibis and Aralan. J. Lab. & Clin. Med. **39**:367 (Feb.), 1952.

Hussey, K. L. and Brown, H. W.: The Complement Fixation Test for Hepatic Amebiasis. Am. J. Trop. Med. **30**:147 (March), 1950.

Iverson, M. K. and Johnson, H. G.: Amebiasis in Food Handlers in San Francisco, J.A.M.A. **108**:875, 1937.

Kullman, H. J. and Schmitt, P. E.: Chronic Ulcerative Colitis in Veterans. J. Michigan M. Soc. **50**:1133 (Oct.), 1951.

Loeb, R. F., Clark, W. M., Coatney, G. R., Coggeshall, L. T., Dieuade, F. R., Dochez, A. R., Hakansson, E. G., Marshall, E. K., Jr., Marvel, C. S., McCoy, O. R., Sapero, J. J., Sebrell, W. H., Shannon, J. A. and Carden, G. A., Jr.: Activity of New Antimalarial Agent, Chrolorquine (Sn-7618). Statement approved by the Board for Coordination of Malarial Studies. J.A.M.A. **130**:1069, 1946.

Monat, Henry A., Capt., M.C., USNR: Intractable Amebiasis—A Warning! Military Surgeon, **99**:310 (Oct.), 1946.

Soderman, W. A.: Diagnostic Aspects of Colonic Amebiasis. M. Clin. North America **36**:405 (March), 1952.

Wright, W. H.: The Public Health Status of Amebiasis in the United States, as Revealed by Available Statistics. Am. J. Trop. Med. **30**:123 (March), 1950.

Zavela, D. C. and Hamilton, H. E.: The Recognition and Treatment of Hepatic Amebiasis. Ann. Int. Med. **36**:110 (Jan.), 1952.

THE RESEARCH APPROACH TO CLINICAL PROBLEMS IN AMEBIASIS*

NORMAN B. McCULLOUGH, Ph.D., M.D.†

Bethesda, Md.

The association of *Endameba histolytica* with human disease was first recognized over three-fourths of a century ago[1], and more than 60 years have passed since the classical work of Councilman and Lafleur[2] definitely defined and established amebic dysentery as a clinical and pathologic entity. In the intervening years a voluminous literature on amebiasis has accumulated. Yet there exists doubt, confusion, and lack of agreement in many major areas of the subject. Concepts of amebiasis vary all the way from the restricted one of "amebic dysentery" to those which attribute numerous and sundry ill defined symptomatologies to the effects of infection with *E. histolytica*. Since the great majority of cases harboring this organism do not have amebic dysentery, or a characteristic syndrome, a clinical diagnosis cannot be made, and even in fulminating cases with typical stools and lesions, laboratory confirmation is necessary to positively establish the diagnosis. Laboratory technics and personnel vary widely in efficiency and dependability. Further, the mere finding of an organism in the stool is no proof that any of the patient's symptoms are referable to it, and when the question of therapy arises, with the many drugs now available, one is really at a loss to find authoritative well controlled studies which may guide him in selecting the regimen of choice. The clinician confronted with the problem or the suspicion of amebiasis in a patient must almost of necessity assume the investigative approach to both the individual patient and to the broad field of amebiasis.

The problems confronting us today in amebiasis are not new, nor are they unique to this disease, but similar to those presented by several of our widespread chronic infectious diseases which may persist in a pateint over long periods of time with manifestations ranging from acute disease with characteristic symptoms and signs to the chronically infected state with practically no definitive findings. Many facets of these questions will be discussed in detail by other members of the panel. This presentation will be limited to presenting an approach to some of the major clinical problems in amebiasis from the standpoint of the clinical investigator. With strong dependence on the laboratory necessitated at every step from diagnosis to cure, there can be no strictly clinical approach to any of these questions, but rather a combined laboratory and clinical attack is necessary.

---

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

†Medical Director, U. S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Microbiological Institute, Chief, Laboratory of Clinical Investigation, Bethesda, Maryland.

Diagnosis

Intestinal Amebiasis:—A thorough search of the stool for *E. histolytica* should be an integral part of every gastroenterologic work-up and a diagnosis of intestinal amebiasis should be made only upon demonstration of the ameba. Immediately we are faced with a major problem. There is no recognized standard method and sampling technic for this examination. We seriously need well controlled studies of the efficiency of the various methods in use for demonstrating amebae in the stool. A battery of the more dependable methods should be used on specimens from a large group of patients to determine their relative efficiency. Studies should be done to determine how many specimens should be examined and what time intervals should be employed to assure a reasonable chance of demonstrating the organism in a high proportion of patients if it is present. Current recommendations based on incomplete knowledge can be only tentative. Using both direct and concentration methods we currently consider that the minimum effort should consist of the examination of five casual stools collected preferably at intervals of several days[3,4,5], and of at least one liquid stool immediately upon passage[6]. In nondiarrheic patients this specimen should be obtained following a saline purge. If suspicious lesions are present at proctosigmoidoscopy direct specimens should be obtained for examination. If all tests are negative and the clinician still entertains a suspicion that the patient may have amebiasis the complete examination should be repeated after several weeks or months.

Extraintestinal Amebiasis:—Usually the diagnosis of extraintestinal amebiasis must be made on clinical grounds considering the history of present or past known or probable intestinal amebiasis. The diagnosis can at times be proved by the finding of amebae in aspirates, drainage material, or operative specimens, but all too often suitable material for direct examination is unobtainable. In such cases a positive complement fixation test yields supportive evidence. Antigen for the complement fixation test and test results vary widely. A standard antigen of proved specificity and a standard technic must be developed, and the question of antigenic strain differences must be resolved before the usefulness and significance of the test results can be appraised. Response to therapy may also provide supportive evidence. Fortunately, the drugs of greatest value against the tissue phases of the ameba do not offer wide microbiological coverage. They are, however, not specific, and the results of such a therapeutic trial must be assessed with caution. In any event, lacking direct confirmation by recovery of the ameba from the patient, the diagnosis can be no more definite than one of presumptive amebiasis.

Indirect diagnostic methods often fail to provide adequate proof of a diagnosis. Further research efforts should be directed toward methods of demonstrating the ameba in extraintestinal lesions; for example by liver biopsy and culture.

General:—If *Endameba histolytica* is found in the stool, all available means should be employed to detect tissue invasion. In addition to the physical examination, a minimal approach should consist of a proctosigmoidoscopic examination, roentgenographic examination of the colon, studies of liver function employing an appropriate battery of tests, and a serum complement fixation test for amebiasis. In cases lacking the characteristic symptomatology of frank amebiasis, that is, the majority of patients who pass cysts and have vague, multiple and inconstant complaints, other disease which might explain their symptoms should be sought for and excluded by appropriate examinations.

Clinical Spectrum of Amebiasis:—If we set aside cases of amebic dysentery, chronic or recurrent diarrhea, hepatitis, liver abscess or other clear-cut extraintestinal localization, and those which provide characteristic ulceration seen at proctosigmoidoscopy, and even those with compatible colonic roentgenologic findings, that is, all cases in which there can be little disagreement or doubt of the etiologic role of the ameba in the patient's illness, we are left with a large group of people with and without symptoms who have *E. histolytica* present in the intestinal tract. A conservative clinical approach demands critical evaluation of the evidence before relating the symptoms of a patient in this group to amebiasis. Other concurrent organic disease should be excluded or brought under proper control. A psychosomatic evaluation of the patient should be made on positive grounds, rather than by exclusion, prior to and subsequent to treatment. The usual caution in clinical evaluation of psychosomatic states should be observed. The evidence for complete eradication of the amebic infection should be rigorous (see remarks on diagnosis and on treatment), and the posttreatment evaluation should be continued for a sufficient period of time to minimize the possible psychotherapeutic effects of treatment. Employing such hind-sight diagnostic appraisal is inescapable in this group of patients.

Pathogenesis:—Possible differences in pathogenicity between strains of amebae need resolution. A great many opinions have been expressed relative to differences in pathogenicity between large and small races of the parasite. The concept that the small race does not produce serious disease and that its presence in a patient can be ignored has not been adequately established by critical studies. Pending further laboratory, epidemiological and clinical studies we are not warranted in accepting this view and should accord such patients the same evaluation and therapy as those harboring the large race. More definite criteria for differentiating the races should be established and studies undertaken to clarify the question of strain differences in relation to pathogenicity and pathogenesis.

Other factors possibly bearing on pathogenesis should be explored, such as the role of diet and associated bacterial flora[7,8].

Factors allowing the development of extraintestinal amebiasis are unknown. With infection of the gastrointestinal tract amebae must reach the liver in great numbers of patients, yet few cases assume clinical importance. Evidence

for liver involvement should be looked for in every such patient. The possibility that permanent fibrotic changes may occur in the liver without clinical evidence of hepatic amebiasis should be explored.

Treatment:—At present, bearing in mind the reservations previously stated, we can but view all patients who are harboring *E. histolytica* as potential if not actual cases of disease. They should all receive treatment.

There is no highly satisfactory treatment for amebiasis. Although a number of drugs provide effective and even dramatic control of acute amebiasis, the relapse rate is often high and toxic side-effects troublesome or even occasionally perilous to the patient. We do not know the mechanism of action on the ameba of the drugs in use. Treatment must be based mainly on empirical knowledge which is far from complete. Even with the older amebicides, differing dosages, treatment periods, combinations of drugs, and criteria of cure render much of the literature difficult to interpret. Well studied series of cases with employment of rigorous and standardized criteria of cure are needed to establish the treatment of choice from our available armamentarium.

Since the drugs effective against the tissue forms of the ameba have relatively little value in rendering the intestinal tract free of the organism, and vice versa, the concept of employing both types of drugs concurrently appears to be most reasonable. In intestinal amebiasis with frank evidence of tissue invasion, clinical studies support this thesis. Whether such combined therapy is warranted in all forms of amebiasis has not been established by controlled clinical studies. Until such data are available the use of combined treatment is consistent with a conservative clinical approach to the therapy of amebiasis.

In assessing the results of therapy it is essential that strict criteria of cure be established. Certainly a patient should become and stay free of all symptoms and signs attributable to amebiasis. Repeat stool examinations at intervals of several weeks with negative findings over a period of one year would seem the minimum requirement in posttreatment follow-up.

REFERENCES

1. Lösch, F.: Massenhafte Entwickelung von Amöben im Dickdarm. Arch. f. Path. Anat., **65**:196-211, 1875.
2. Councilman, W. T. and Lafleur, H. A.: Amebic Dysentery. Johns Hopkins Hosp. Report, **2**:395-548, 1891.
3. Faust, E. C.: Modern Criteria for the Laboratory Diagnosis of Amebiasis. Am. J. Trop. Med. & Hyg., **1**:140-145, 1952.
4. Tobie, J. E., Reardon, L. V., Bozicevich, J., Shih, B. C., Mantel, N. and Thomas, E. H.: The Efficiency of the Zinc Sulfate Technic in the Detection of Intestinal Protozoa by Successive Stool Examinations. Am. J. Trop. Med., **31**:552-560, 1951.
5. Hood, M., Sodeman, W. A. and Akenhead, W. R.: Comparison of the Effectiveness of the Examination of Multiple Stools and Proctoscopic Material for the Detection of Amebiasis. Am. J. Trop. Med. & Hyg., **1**:539-542, 1952.
6. Shookhoff, H. B.: Amebic Dysentery. Rev. Gastroenterol., **19**:48-55, 1952.
7. Stewart, G. T.: The Role of Bacteria in Intestinal Amebiasis in Man. Ann. Trop. Med. & Parasit., **42**:198-206, 1948.
8. Stewart, G. T., Jones W. R. and Rogers, M. A. T.: *Streptococcus faecalis* in *E. histolytica* Infections. Nature, **161**:936, 1948.

THE LABORATORY APPROACH TO PROBLEMS IN AMEBIASIS*

WILLARD H. WRIGHT, Ph.D.†

Bethesda, Md.

Within the past few years laboratory research has contributed materially to knowledge concerning many phases of amebiasis. It is true that the study of certain fundamental problems has been hampered by inability to cultivate *Endameba histolytica* without bacteria and to establish fulminating infections in small laboratory animals, but these difficulties have now been partially overcome. In the few minutes available, we should like to review some of the laboratory investigations of interest to the gastroenterologist.

Diagnosis:—The zinc sulfate centrifugal flotation technic[1] with modifications and improvements[2] has proved to be an effective method for concentrating ameba cysts for diagnostic purposes. A more recent method, formalin-ether sedimentation[3], is claimed to have certain advantages over the zinc sulfate technic. Stools forwarded to distant points for examination may be preserved by the PVA fixative of Brooke and Goldman[4] or the "MIF" solution of Sapero and Lawless[5].

During recent years, considerable effort has been made to produce more potent and specific antigens for the complement fixation test for amebiasis[6,7]. Success has not been entirely achieved. While the test is of considerable value in cases of extraintestinal infection, it would appear that in many cases of intestinal involvement the amount of tissue penetration is not sufficient to stimulate antibody production to the point of serological detection.

Metabolism of E. histolytica:—While this may seem to be only of academic significance, actually a more complete knowledge of the subject might contribute materially to certain clinical problems. The cultivation of the organism by Boeck and Drbohlav[8] in 1924 was a great step forward. Since, however, such cultivation was accomplished only with the concomitant bacterial flora of the stool, little information concerning the metabolism of the ameba could be derived from such cultures. Cysts of *E. histolytica* have been isolated free of bacteria by chemical means[9] and microisolation[10], and such cysts have been established in culture with single species of bacteria. While this accomplishment represented some advance, it failed to provide bacteria free cultures. Through the use of antibiotics[11] some growth of ameba was obtained with dead bacteria. A further step forward was accomplished when Phillips[12] succeeded in cultivating the ameba with *Trypanosoma cruzi*, and when Shaffer et al[13] were able to propagate the organism in a chick-embryo tissue-bearing substrate.

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

†Chief, Laboratory of Tropical Diseases, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Microbiological Institute, Bethesda, Maryland.

With these and other tools, some progress has been made in elucidating the metabolism of the ameba. No one, however, has succeeded in inducing axenic growth of the ameba in a chemically defined medium; until this is done metabolic studies will still be handicapped.

Virulence of strains:—Variations in the pathogenicity of *E. histolytica* have long been thought to be associated with differences in the virulence of strains. Small cyst strains are believed by some authorities to be less virulent than large cyst strains. Meleney and Frye[14] have demonstrated that in cats differences in pathogenicity are exhibited by various strains. Other investigators have made similar observations in other animals. Difficulties are frequently encountered in our laboratory in maintaining the virulence of different strains for infecting laboratory animals. It has been shown[15,16] that prolonged cultivation of the ameba with *Trypanosoma cruzi* resulted in a complete loss of virulence for rabbits and guinea pigs. Virulence was restored by returning the ameba to cultures with a mixed bacterial flora. Thus it would seem that virulence may in some way be associated with the concomitant bacteria.

The importance of the bacteria-ameba relationship:—It has been seen that bacteria are of importance for the growth and the maintenance of virulence of *E. histolytica*. Recent studies by Phillips et al[17], in cooperation with the Lobund Institute, University of Notre Dame, have shown that *E. histolytica* grown with *T. cruzi* and injected into the cecum of germ-free guinea pigs failed to produce any lesions and rapidly died out; nearly all conventional control guinea pigs succumbed following infection with the same material. When the germ-free guinea pigs were fed orally with either *Escherichia coli* or *Aerobacter aerogenes* prior to cecal inoculation with the ameba, typical ulcerative amebiasis was produced. The question thus arises as to how much of the success of antibiotic therapy may be due to the effect of the treatment on the bacteria.

Influence of nutrition on pathogenicity:—There is some evidence that nutrition may influence the symptomatology of amebiasis. Elsdon-Dew[18] has pointed out that in the Bantu population in Durban, South Africa, there is a high incidence of acute fulminating rapidly fatal amebic dysentery, whereas this form of the disease is not seen in the European or Indian inhabitants of the area. He attributes such differences to the high maize diet of the Bantu. Felsenfeld and Comess[19] believed that the parasites were reduced under a high protein-low carbohydrate diet. While much more work needs to be done, certain laboratory studies have indicated that diet may play an important role in the pathogenicity of the ameba. Whether this influence is exerted on the ameba or the bacteria or both is not known.

Modes of transmission:—There is practically no information available concerning the degree of exposure necessary to establish an amebic infection. Some clue to the ease with which transmission may be accomplished was furnished by the experiments of Rendtorff et al, who exposed human volunteers to *Endameba coli*, even though it is possible that *E. histolytica* may not be equally

infectious. Of 26 men, 8 or 30.8 per cent, developed *Endameba coli* infections after receiving from 1 to 10,000 cysts administered orally in gelatin capsules[20]. One volunteer developed an infection after receiving a single cyst, and three were infected after a dosage of 10 cysts each. Infections were produced in 70.6 per cent of 20 volunteers by the addition of 100 cysts each of *E. coli* to the drinking water[21]. None of 18 volunteers became infected when 127 flies, exposed to cysts of *E. coli,* were released in a kitchen-dining room. One man became infected when exposed flies were placed directly on the food[22].

Lack of sewage treatment or inadequate treatment may be the means of contaminating water supplies with cysts of *E. histolytica.* Laboratory research indicates that certain sewage treatment processes are effective in preventing transmission of amebiasis while others are not[23]. Primary sedimentation did not remove cysts of *E. histolytica* from sewage; the cysts passed through the trickling filter and survived activated sludge treatment. Sludge digestion was inimical to the cysts; chemical precipitation was effective in removing them during secondary settling as was filtration through a 24-inch layer of sand at a rate of 100,000 gallons per acre per day.

Prophylaxis:—Laboratory studies have indicated that superchlorination or superiodation for a period of at least 30 minutes is necessary for the destruction of cysts of *E. histolytica.* Methods have been worked out for the protection of troops in the field. Studies by Beaver and Deschamps[24] and Jones[25] indicate that ameba cysts on vegetables are destroyed by a 5 per cent solution of acetic acid for 15 minutes at a temperature of 30°C. or by 5 minutes exposure of 2.5 per cent acetic acid at 45°C.

Chemotherapy:—In developmental chemotherapy, new approaches are available in the *in vitro* test with cultures of *E. histolytica-T. cruzi*[26] and through the adaptability of the ameba to laboratory animals by various investigators[27,28,29]. Monkeys, dogs, rats, rabbits, and guinea pigs have been utilized for drug screening. Rats have not been satisfactory in the hands of most investigators. Guinea pigs have proved advantageous in our laboratory. Of course, no laboratory animal test can supply the final answer concerning the efficacy of any compound in the human host, but animal testing is advantageous in providing compounds of potential clinical value.

REFERENCES

1. Faust, E. C., Sawitz, W., Tobie, J., Odom, V., Peres, C. and Lincicome, D. R.: Comparative efficiency of various technics for the diagnosis of protozoa and helminths in feces. J. Parasitol. **25**:241-262, 1939.
2. Tobie, J. E., Reardon, L. V., Bozicevich, J., Shih, B. C., Mantel, W. and Thomas, E. H.: The efficiency of the zinc sulfate technic in the detection of intestinal protozoa by successive stool examinations. Am. J. Trop. Med. **31**:552-560, 1951.
3. Ritchie, L. S., Pan, C. and Hunter, G. W. III: A comparison of the zinc sulfate and the MGL (Formalin-Ether) technics. J. Parasitol. **38**: Sec. 2, 16, 1952.
4. Brooke, M. M. and Goldman, M.: Polyvinyl alcohol fixative as a preservative and adhesive for protozoa in dysenteric stools and other liquid materials. J. Lab. & Clin. Med. **34**:1554-1560, 1949.

5. Sapero, J. J. and Lawless, D. K.: The "MIF" stain-preservation technic for the identification of intestinal protozoa. Am. J. Trop. Med. & Hyg. **2**:613-619, 1953.
6. Rees, C. W., Bozicevich, J., Reardon, L. V. and Jones, F. E.: A preliminary note on the complement fixation test for amebiasis with antigens prepared from *Endameba histolytica* grown with a single species of bacteria. Am. J. Trop. Med. **22**:581-586, 1942.
7. Fulton, J. D., Joyner, L. P. and Orpwood Price, I. N.: Studies on protozoa. Part IV. A complement fixation test for amebiasis. J. Trop. Med. & Hyg. **54**:27-33, 1951.
8. Boeck, W. C. and Drbohlav, J.: The cultivation of *Endameba histolytica*. Am. J. Hyg., **5**:371-407, 1925.
9. Meleney, H. E., Frye, W. W., Leathers, W. S. and Snyder, T. L.: The sterilization of cysts of *Endameba histolytica*, with preliminary observations on excystation. Proc. 3d Internat. Cong. Microbiol. pp. 410-411, 1940.
10. Rees, C. W.: The construction of a micromanipulator for the isolation of protozoa. Am. J. Trop. Med. **22**:487-492, 1942.
11. Jacobs, L.: The elimination of viable bacteria from cultures of *Endameba histolytica* and the subsequent maintenance of such cultures. Am. J. Hyg. **46**:172-176, 1947.
12. Phillips, B. P.: Cultivation of *Endameba histolytica* with *Trypanosoma cruzi*. Science, **111**:8-9, 1950.
13. Shaffer, J. G., Sienkiewicz, H. S. and Washington, J. E.: The propagation of *Endameba histolytica* in tissue-bearing culture without accompanying bacteria or other microorganisms. Am. J. Hyg. **57**:366-379, 1953.
14. Meleney, H. E. and Frye, W. W.: Studies of *Endameba histolytica* and other intestinal protozoa in Tennessee: IX. Further observations on the pathogenicity of certain strains of *E. histolytica* for kittens. Am. J. Hyg. **21**:422-437, 1935.
15. Luttermoser, G. W. and Phillips, B. P.: Some effects of cultural associates on the infectivity of a strain of *Endameba histolytica* for the rabbit. Am. J. Trop. Med. & Hyg.,**1**:731-735, 1952.
16. Phillips, B. P. and Bartgis, I. L.: Effects of growth *in vitro* with selected microbial associates and of encystation and excystation, on the virulence of *Endameba histolytica* for guinea pigs. Am. J. Trop. Med. & Hyg. **3**:621-627, 1954.
17. Phillips, B. P., Wolfe, P. A., Rees, C. W., Gordon, H. A., Wright, W. H. and Reyniers, J. A.: Studies on the ameba-bacteria relationship in amebiasis. Comparative results of the intracecal inoculation of germ-free, monocontaminated, and conventional guinea pigs with *Endameba histolytica*. Am. J. Trop. Med. & Hyg. In press, 1955.
18. Elsdon-Dew, R.: Endemic fulminating amebic dysentery. Am. J. Trop. Med. **29**:337-340, 1949.
19. Felsenfeld, O. and Comess, O.: Dietary management of amebiasis. Proc. Am. Fed. Clin. Res. **3**:8, 1947.
20. Rendtorff, R. C.: The experimental transmission of human intestinal protozoan parasites. I. *Endameba coli* cysts given in capsules. Am. J. Hyg., **59**:196-208, 1954.
21. Rendtorff, R. C. and Holt, C. J.: The experimental transmission of human intestinal protozoan parasites. IV. Attempts to transmit *Endameba coli* and *Giardia lamblia* by water. Am. J. Hyg. **60**:327-338, 1954.
22. Rendtorff, R. C. and Holt, C. J.: The experimental transmission of human intestinal protozoan parasites. III. Attempts to transmit *Endameba coli* and *Giardia lamblia* cysts by flies. Am. J. Hyg. **60**:320-326, 1954.
23. Cram, E. B.: The effect of various treatment processes on the survival of helminth ova and protozoan cysts in sewage. Sewage Works J. **15**:1119-1138, 1943.
24. Beaver, P. C. and Deschamps, G.: The effect of acetic acid on the viability of *Endameba histolytica* cysts. Am. J. Trop. Med. **29**:193-197, 1949.
25. Jones, M. F.: Studies on treatment of fresh vegetables contaminated with cysts of *Endameba histolytica*. I. Acetic acid. Am. J. Trop. Med. & Hyg. **1**:576-584, 1952
26. Phillips, B. P.: Measurements of direct amebicidal potential by a micro-method for the screening of drugs *in vitro*. Am. J. Trop. Med. **31**:561-565, 1951.
27. Tobie, J. E.: Experimental infection of the rabbit with *Endameba histolytica*. Am. J. Trop. Med. **29**:859-870, 1949.
28. Carrera, G. M. and Faust, E. C.: Susceptibility of the guinea pig to *Endameba histolytica* of human origin. Am. J. Trop. Med. **29**:647-668, 1949.
29. Taylor, D. J., Greenberg, J. and Coatney, G. R.: Experimental infection of guinea pigs with *Endameba histolytica*. J. Parasitol. **35**: Sec. 2, 24, 1949.

FACTORS RELATED TO THE PATHOGENICITY OF ENDAMEBA HISTOLYTICA*

CHARLES W. REES, B.S., M.A., Ph.D.†

Bethesda, Md.

Although the factors involved in the pathogenicity of *Endameba histolytica* have provided material for debate for more than three-quarters of a century, since the first documented case of clinical amebiasis was described by Loesch (1875), there is still no unanimity of opinion concerning them. During the short time allotted to the present discussion it will be possible only to indicate some of the points at issue and to present some of the arguments regarding their relative importance. The factors herein selected are those discussed in the pioneer publication by Loesch, the classic monograph of Dobell (1919), the paper by Craig (1927) and some recent investigators on amebiasis of experimental animals.

Probably the least biased of any of the opinions in the literature were those of Loesch. His data were obtained from the patient's history of illness extending over a period of more than three years, from study of the case by Loesch and his colleagues during approximately six months of the patient's hospitalization to his death, and from study of an experimentally infected dog. Since the patient had spells of severe dysentery, alternating with remissions, Loesch examined the stools microscopically with what at the time was considered an astounding discovery that the dysenteric stools were teeming with amebae. The numbers of this parasite increased tremendously immediately prior to and during each bout of dysentery and decreased during periods of remission, at some times being demonstrable only on prolonged search. Loesch observed further that the amebae were not uniformly distributed throughout the dysenteric stool but were concentrated in flecks of blood-tinged mucus. He noted also that ingested erythrocytes were frequently demonstrable in the amebae and that ingested cocci, bacilli, and other forms of bacteria were generally present.

In view of the correlation between the presence of amebae and the occurrence of the dysenteric symptoms and the finding of many ulcers and other lesions in the colon and rectum at autopsy, Loesch expressed the opinion that the relationship was causal despite emphatic statements previously made by distinguished protozoologists including Leuckart that amebae could never be parasites. In the spirit of a true scientist, however, he sought confirmation of this viewpoint from experiments on dogs. He was considerably dismayed by the occurrence of severe illness in all of four dogs inoculated *per os* and/or *per*

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

†Laboratory of Tropical Diseases, U. S. Department of Health, Education, and Welfare, Public Health Service, National Institutes of Health, National Microbiological Institute, Bethesda, Maryland.

anum with from one to several ounces of dysenteric feces, and by abatement of the illness after several days with only one case of infection by amebae. The prepatent period was approximately eight days, the dog passed stools containing flecks of blood and mucus heavily laden with amebae but recovered spontaneously several days later. On the 20th day when the dog was sacrificed there were several minor lesions in the colon and rectum, but they were very mild compared with those in the human patient. Therefore, in the concluding statement of the publication, Loesch expressed the opinion that the initial diarrhea and dysentery of the patient were of bacterial etiology, and that the ameba had functioned primarily in preventing healing of the lesions.

Because of this final statement and the fact that the immediate cause of death of the patient was severe caseous pneumonia, and particularly because the amebae contained numerous bacteria, the scientific value of this pioneer work has not been appreciated by many recent students of amebiasis. Some have even expressed the opinion that Loesch's patient was infected with the nonpathogenic *Endameba coli* rather than *E. histolytica*. Much of the skepticism is attributable to statements of Dobell (1919) in his world-renowned monograph. Although Dobell furnished excellent descriptions and figures of the four commensal species of amebae as well as of the pathogenic *E. histolytica* from the digestive tract of man, he made several assertions that have had a profound influence on the thinking of subsequent investigators even to the present time. He stated: 1. that *E. histolytica* obtains nourishment only by absorption from living tissues of the host, 2. that within the host it never ingests bacteria, and 3. that it probably would never be cultivated *in vitro*, despite a previous demonstration of cultivability by Cutler (1918). Certainly the third and most probably the first and second of the above opinions are mainly of historic interest at the present time. For example, Hoare, 1952 in confirmation of the early work by Loesch has demonstrated ingestion of bacteria by *E. histolytica in vitro* as well as *in vivo*.

The influence of the first and second assertions, which are corollary to each other, has been reflected in a number of ideas held rather widely among students of amebiasis. For one thing, the opinion has been held that *Endameba histolytica* is always a pathogen; that even in nondysenteric cases minute pinpoint ulcers are present in the intestine of infected humans. Obviously, if *E. histolytica* were to obtain nutrients only from the living tissues of its host, some destruction of these tissues would have to be apparent. Craig (1927) concluded that the living ameba carries a hemolysin and a cytolysin, which are important factors in the pathogenicity of *E. histolytica*. He based his arguments on experiments with alcoholic extracts and, incidentally, stated that the lack of bacteriolytic activity of these alcoholic extracts was correlated with the failure of the ameba to ingest bacteria *in vivo*. The question of the presence of such lysins requires study by more exact methods which may become available with the improvement in technics of cultivation. At the present time, it is best to emulate the open-mindedness

of Loesch rather than to rely too heavily on the statements of later authorities, which have not been adequately verified.

Recent work by Luttermoser and Phillips (1952), Phillips and Bartgis (1954) and as yet unpublished data by Taylor and associates, of the Laboratory of Tropical Diseases of National Microbiological Institute indicates that bacteria occurring in cultures of *E. histolytica* are of considerable importance in the development of dysentery in rabbits and guinea pigs. Using a highly pathogenic culture of *E. histolytica,* designated as strain 200 (Tobie, 1949), Luttermoser and Phillips produced amebic dysentery in 106 of 126 rabbits that were injected intracecally with amebae from cultures with a mixed bacterial flora, in 17 of 34 injected with the same strain of monoxenic culture with organism *t,* and in only 1 of 24 that were injected with another monoxenic culture of the same strain with *Trypanosoma cruzi.* Although Phillips and Bartgis, using guinea pigs on a special diet, obtained infection with the 200 strain in 124 animals out of 364 that were injected with ameba-cruzi, none of these animals had lesions, in sharp contrast with results generally obtained from cultures with a mixed bacterial flora.

In their entirety the data obtained during the past several years on experimental inoculation of rabbits and guinea pigs support the final conclusion by Loesch to the effect that bacteria may function in the pathogenicity of *E. histolytica.* Obviously, however, the bearing that pathogenicity in these animals which differ physiologically and in many other ways from man, may have on human clinical amebiasis requires careful study. Many factors of the infection in man such as changes of diet, of climate, and of physiological conditions may be of great importance but cannot be considered in detail in the present discussion. The present-day rareness of cases of clinical amebiasis in populations having high sanitary standards, living on vitamin-rich foods compared with the high incidence of such cases at and before the turn of the century indicates that many factors are operative in the pathogenicity of *E. histolytica.* The principal danger lies in the indifference that now prevails in many quarters to the seriousness of the disease. Well conducted investigations have shown that cases of amebic dysentery, and/or extraintestinal amebiasis may be overlooked or diagnosed as malignancies, disorders of the liver, or as infections attributed to other agents than *E. histolytica.*

BIBLIOGRAPHY

Craig, C. F.: Observations upon the hemolytic, cytolytic, and complement-binding properties of extracts of *Endameba histolytica.* Am. J. Trop. Med., **7**:225-240, 1927.

Cutler, D. W.: A method for the cultivation of *Endameba histolytica.* J. Path. & Bact., **22**:22-27, 1918.

Dobell, C.: The Ameba Living in Man. 155 pp. John Bale Sons & Danielsson, Ltd. London, 1919.

Hoare, C. A.: Parasitological reviews. The commensal phase of *Endameba histolytica.* Exper. Parasitol., **1**:411-427, 1952.

Loesch, F.: Massenhafte Entwickelung von Ameben im Dickdarm. Virchow's Arch. Path. Anat., **65**:196-211, 1875.

Luttermoser, G. W. and Phillips, B. P.: Some effects of cultural associates on the infectivity of a strain of *Endameba histolytica* for the rabbit. Am. J. Trop. Med. & Hyg., **1**:731-735, 1952.

Phillips, B. P. and Bartgis, I. L.: Effects of growth *in vitro* with selected microbial associates and of encystation and excystation on the virulence of *Endameba histolytica* for guinea pigs. Am. J. Trop. Med. & Hyg., **3**:421-627, 1954.

Tobie, J. E.: Experimental infection of the rabbit with *Endameba histolytica*. Am. J. Trop. Med. **29**:859-870, 1949.

CLINICAL ASPECTS OF AMEBIASIS WITH OBSERVATIONS ON VARIATIONS IN TROPICAL AND TEMPERATE ZONES*†

CLARENCE A. IMBODEN, Jr., M.D.

and

HENRY K. BEYE, M.D.

Bethesda, Md.

It is difficult to offer a description of clinical intestinal amebiasis that will be acceptable to all interested parties. One school of thought emphasizes the vagueness and nonspecificity of symptoms by which the infection is manifested in some patients. Another feels that these aspects have already been given a disproportionate emphasis and resists accepting the broad spectrum of vague complaints often attributed to amebiasis[1,2].

Considering the lack of definitive knowledge concerning the determinants of the pathogenicity of *Endameba histolytica*, one cannot take an inflexible stand regarding the range of symptoms the infection may produce. For the present, the wisest course seems to be to think of a possible amebic etiology in a wide variety of complaints, and then proceed to rule it in or out, as best one can.

"Temperate" Zones—North America

Prevalence:—A brief look at the great variation of reported prevalence rates in various sections of North America affords an insight into the difficult matter of ascertaining the magnitude of the amebiasis problem here. Wright (1950)[3] reviewed the public health statistics on the infection, and pointed out the many factors to be considered in their interpretation. Certainly *some* of the differences in the figures reported are due to the differences in the index of suspicion in the clinical area. Reports from gastroenterologists, parasitologists and others range from 17 per cent of unselected hospital patients in Memphis to 0.046 per cent in New York City [1,4-10]. The absence of strict and standard criteria of diagnosis and cure in amebiasis made the evaluation of the data difficult.

Prevalence rates among veterans range from 10.1 per cent of those with domestic service only, to 28.3 per cent of those serving in the China-Burma-India Theatre. Some reports indicate the highest rates among those returning from the Pacific Theatre of Operations, but this difference was not noted in all veteran surveys[6,11-16].

---

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

†From the U. S. Department of Health, Education and Welfare, Public Health Service, National Institute of Health, National Microbiological Institute, Laboratory of Clinical Investigation.

Among children, Loeber and D'Antoni (1947)[17] found 73 cyst-passers in four months of regular office practice in New Orleans. Goldenberg, et al (1952)[18] found a significant prevalence among infants in Chicago though the actual rates were far lower than in the New Orleans report. In Canada, reports are available of infections with *E. histolytica* among approximately 37 to 50 per cent of orphanage children[19,20]. Institutional rates in general tend to be considerably higher than in the general population[28,29].

Manifestations:—It is clear that many individuals infected with *E. histolytica* show no evidence of disease. In treatment study reports, it is common to find that approximately one-third of these patients in our civilian population exhibit signs and symptoms of gastrointestinal disease in significant degree[5,31,32,33]. In a large series of outpatients seen in a gastroenterologic practice, Browne, McHardy and Spellberg (1945)[4] reported that 15.7 per cent had acute or chronic dysentery and 84.3 per cent fell into the "carrier" category. In their paper, the "carriers" were subdivided into an asymptomatic group and an "enteric-symptomatic" group, the latter including those with somewhat vague and nonspecific enteric complaints. This report and others have emphasized the variable clinical picture and the occurrence, in significant numbers, of patients suffering from organic colonic pathology without manifesting any notable symptoms[6,23,27]. In these papers, amebic hepatitis occurred in about 6 per cent of the total number of infections, with amebic liver abscess in about 2 per cent. Albright and Gordon[22], however, estimate active liver involvement in about one-third of all cyst passers. Amebic hepatic disease will be discussed further below.

All clinical reports in North America indicate the infrequent occurrence of frank dysentery in endemic amebiasis and many observers ascribe a host of systemic complaints due to the infection. Malnutrition and retarded development secondary to anorexia and poor digestion, headache, vasomotor instability and other symptoms referable to the autonomic nervous system are found associated with amebiasis and often ameliorate after therapy[24,25,26,32,36]. Rappaport, et al, described the association of polyarthritis with intestinal amebiasis and found good clinical response following eradication of the infection[37]. Allergies manifested by skin rashes or asthma have been described[34].

Among rural populations, Alexander and Meleney[8] found a high prevalence rate of true dysentery in a hill community in Tennessee. In the area, economic conditions were generally poor, and the diet was inadequately balanced. Carbohydrate in the form of corn-meal supplied the bulk of the caloric needs. In a control study of a more prosperous bottomland community, frank dysentery was far less frequent, although the infection rate was actually higher. The greater pathogenicity in the former was attributed to the poor diet. No adequate explanation for the greater infection rate in the healthier community has been advanced.

Many clinical studies have been published covering the experience with veterans or active military personnel, and, in general, the percentage of symptomatic disease tends to be higher than in civilians. There are many exceptions, however, and the data between the two large areas may not be entirely comparable. In 58 cases described by Spellberg and Zivin[15], only 14 were essentially asymptomatic and in the remainder gastrointestinal symptoms ranged from mild to severe. A rather high proportion of hepatic involvement was found with seven patients exhibiting amebic hepatitis and eight with frank amebic abscess of the liver. In this group, veterans from the Pacific Theatre of Operations had the highest rate of liver disease, and this was attributed to a higher strain virulence. This observation, however, did not hold in other series[11].

In forty cases studied by Palmer[14], only three were asymptomatic. Seventy per cent had symptomatic uncomplicated amebic colitis manifested by anorexia, nausea, vomiting, lower abdominal cramps, and periodic diarrhea. 17.5 per cent had hepatic amebiasis. Multiple amebomata were found in one. Other reports showed a similar distribution of findings[34,35].

The extent of the amebiasis problem among children is as difficult to assess as in adults. Loeber and D'Antoni[17] found nonspecific systemic complaints in most of their patients, with relatively few showing diarrhea or dysentery. They found that the organism was often missed by examination of a normally passed or purged stool and was often found only by proctoscopic aspiration. If this holds for most of the young amebiasis victims elsewhere, then certainly the diagnosis is frequently missed. Miller[19], however demonstrated the organism in the stools of a rather high percentage of the children in his orphanage studies. In his series, again the frequent occurrence of systemic complaints, notably fatigue and anorexia was prominent. Underdevelopment, physical and mental, and a generally poor nutritional status were commonly associated with amebiasis and responded well to antiamebic therapy. Goldenberg[18] et al, investigated infantile diarrhea in Chicago, and found that 9.2 per cent of their cases were attributable to *E. histolytica*. The clinical symptomatology ranged from mild to very severe.

Complications:—Hepatic Amebiasis:—During active amebic colitis, *E. histolytica* trophozites most probably metastasize to the liver via mesenteric venules, the majority of them reaching the right lobe of the liver due to the hemodynamics of the venous drainage from the right colon. Our knowledge of the sequence of events subsequently is not complete. It appears reasonable, however, to assume that in the vast majority of instances, the amebae fail to survive and to establish infection there. It is commonly noted that a moderate degree of tender or nontender hepatomegaly often accompanies acute and chronic intestinal amebiasis, without other clinical or laboratory evidence of hepatic involvement. It is the usual experience to observe the resolution of this finding upon successful treatment of the bowel infection, even though the drug used is active only within the

bowel lumen. It is moot as to whether this manifestation of amebiasis is actually related to true hepatic amebiasis.

In many instances, the diagnosis of hepatic amebiasis (hepatitis or abscess) must be made on clincal grounds plus serologic support, without actual identification of the organism. The general clinical picture, characteristic leucocytosis, x-ray findings, positive complement fixation reaction and response to specific therapy usually constitute the evidence from which the diagnosis is made. The stools are often negative for the parasite and a past history suggestive of amebiasis is often absent.

The clinical features of acute amebic hepatitis and abscess have been well described elsewhere[38-41] and require no repetition here. It may be appropriate to point out however that in certain instances, presenting findings may be atypical and surprisingly devoid of localizing features[42]. In instances of abscess in the caudate lobe, many characteristic physical diagnostic and x-ray signs are absent and the diagnosis is often unsuspected until revealed by exploratory laparotomy. The use of penumoperitoneum x-ray technics is sometimes necessary to localize the abscess.

Other complications of amebiasis are relatively rare in this country. Pulmonary involvement is usually secondary to active hepatic lesions but primary hematogenous pulmonary foci do occur. Brain abscess is practically always found only in the presence of pre-existing combined pulmonary and hepatic lesions.

In a study of complications of amebiasis, Simmonds[43] reviewed the autopsies of 19 cases at Northwestern University and surveyed the literature. The most common serious complications involved hepatic amebiasis and accidents secondary to severe bowel ulcerations such as peritonitis with or without rupture. In epidemic form (Chicago, 1933), fatal complications led to a 7 per cent mortality. Complications rare enough to be considered curiosities include rectovaginal fistulae, prostatic involvement, thrombosis of the vena cava or renal vein, pylephlebitis, cutaneous amebiasis and abscesses of the spleen, ovary, testes and kidney. Severe hemorrhage is uncommon.

In approaching that part of our topic which compares amebiasis in temperate and tropical zones, it is well to consider briefly the connotations of the term "tropical". Considered geographically, the tropics lie between the lines of Cancer and Capricorn. But within this vast zone, climate and weather vary widely. Many areas in the tropics have ideal, truly temperate climes. The hot, humid, doldrum-producing climate actually occurs only in limited areas. From the climatological viewpoint, the tropics are far too heterogeneous to be considered as a whole[44]. On the other hand, especially when applied to medical concepts, the term "tropical" often brings to mind large populations with few sanitary practices who are burdened with a variety of protozoan and metazoan parasites with complex life cycles as well as cosmopolitan diseases. Thus we

find that "tropical diseases" are of considerable importance in such geographically non-tropical areas as Korea, Japan, and North Africa.

With a cosmopolitan disease, such as amebiasis, it may be expected then that there are few essential differences between the manifestations as they appear in the two great areas. Some differences may be more apparent than real in that the less dramatic infections receive less attention. When tropical distinction does seem to exist, it may be due to factors other than the tropical location *per se*.

The continent of Africa, stretching well beyond the northern and southern confines of the tropics, affords a good opportunity to compare the manifestations of amebiasis in and out of the tropics, as strictly defined.

North Africa

North Africa, sharing latitudes with New Orleans (Cairo) and San Francisco (Tunis), presents a highly variable picture. Factual epidemiological data are limited through many North African countries[45] but clinical literature is plentiful. In Algiers, the clinical picture apparently resembles that seen in North America, with nondysenteric intestinal amebiasis rather frequently seen and relatively common extraintestinal complications[46]. In Tunisia, amebic liver abscess is reported to be rather rare; Corcos[47] encountered only six authentic cases during twelve years of experience there. Schneider and Dupoux[48] found Parisian and Tunisian strains responding equally well to various chemotherapeutic agents. Payet[49] found that North African strains are of mild virulence and respond better to treatment than those of Equatorial Africa and Indochina.

In Morocco, clinical amebiasis is apparently not a serious problem among the indigenous population. Barley plays a prominent role in local diets and some have attributed to it a beneficial effect against *E. histolytica*. At any rate, the infection is usually asymptomatic among the reasonably well-nourished population, and rather severe among the undernourished weanlings who also have kwashiorkor. Among local Europeans, clinical amebiasis is quite common during their first two months in the area. Extraintestinal amebiasis is rather rare in both groups[50].

In Egypt, Halawani[51] reports that prevalence rates are highly variable (from 30 to 85 per cent) in and around Cairo, depending on the sanitary practices of the various localities. Small race *E. histolytica* (cysts 9 microns or less in diameter) constituted a large majority of the infections. Even with a high carrier rate, however, only 1.9 per cent of 8,039 patients studied in 1949 exhibited frank dysentery. In an Alexandria hospital, of 1,379 autopsies, only 27 cases had amebic intestinal lesions and 8 had liver abscesses.

El Mofty and Moussa[52] reviewed experiences with 850 patients over a five-year period and the distribution of acute, chronic and asymptomatic cases, and

those with hepatic complications, compares closely with similar North American reports.

Therapeutic response to the newer amebicides is comparable to that in this country[53,54,55].

Tropical Africa

A brief literature review from several countries in tropical Africa readily illustrates the lack of uniformity in regard to clinical amebiasis. In Ethiopia, prevalence of infection varies from 7 to 60 per cent, with acute disease occurring chiefly in plateau regions[45]. In Addis Ababa, high in the mountains, Rizzotti[56] reports that in three years, he treated 442 patients whose symptoms varied from mild diarrhea to severe dysentery. Approximately 7 per cent of the patients carried small race *E. histolytica*, and these were essentially asymptomatic.

In French West Africa, acute amebic dysentery is a serious problem among natives and Europeans in urban areas. Extraintestinal amebiasis is common in both populations. Treatment is more difficult than generally experienced in the U. S. A. and oxytetracycline, given alone, frequently fails[57]. More response is shown to some of the new arsenicals such as diaphetarsine[58].

Reports from the vast territory in eastern Africa disclose that the full range of severe intestinal lesions and complications is common. In recent years, however, apparently because of improved methods of treatment, the incidence of hepatic complications is decreasing[59].

The Belgian Congo encompasses a great variety of terrain and climate. No less variable are the clinical manifestations of amebiasis. In Leopoldville symptomatic enteric disease is common and hepatic amebiasis is not rare. All clinical grades of severity are seen but therapeutic responses are generally satisfactory. Stanleyville, situated in the equatorial rain forests, harbors a severe form of dysentery, with frequent and severe hepatic lesions. By contrast, in Elisabethville, near the southernmost border of the Belgian Congo, amebiasis is rarely seen in any clinical form. Here, the climate is somewhere between temperate and subtropical most of the year.

South Africa

It remains, however, for the area of Durban in the Union of South Africa, some 500 miles below the Tropic of Capricorn, to present what may be the most acute and fulminating amebic dysentery in all Africa. There the climate is described as tropical in the summer. In this area, amebic colitis is extremely common and often intractable as it occurs in the native Bantu. Among the large Hindu segment of the population, acute disease is far less prominent and even less so among the European[60].

In the Bantu, the onset of dysentery is abrupt and explosive. The degree of colonic and rectal tissue damage is readily reflected in the microscopic characteristics of the stool: little fecal material, large numbers of leucocytes, erythrocytes and mucosal shreds. The exudate is quite similar to that commonly seen in bacillary dysentery. Proctoscopic findings correlate well with the fecal smear.

The great difference between the clinical picture in the Bantu and the Hindu (although fecal contamination is great in both groups) stimulates considerable speculation concerning the pathogenicity of *E. histolytica*. The total incidence of amebiasis and other diseases due to enteropathogens is essentially the same among the Bantu and the Indian, but only in the former is the fulminating amebic disease found. The most attractive hypothesis indicates that diet may be the prime determinant of pathogenicity. The chief staple of the Bantu is maize and protein-deficiency is the rule among those that migrate to the urban area. In his more natural environment, the Bantu enjoys a more balanced diet and amebiasis is far less severe. The Hindu diet is largely curry and rice. The European diet is balanced.

Major grades of dysentery are extremely uncommon in the European population and hepatic amebiasis virtually unknown. In the Hindu at Durban, severe dysentery is rare but liver involvement rather frequent. In the Bantu, both are common and the death rate approaches 10 per cent for acute cases[3,61]. Total prevalence rates among the Bantu in the area, however, are rather surprisingly low, Elsdon-Dew reporting them to be about 10 per cent[62].

Treatment of the acute disease is far from satisfactory but the advent of wide-spectrum antibiotics, used there chiefly with older amebicides, have brought considerable improvement. Although beneficial in controlling the acute attack, chlortetracycline and oxytetracycline therapy has a relapse rate of about 14 per cent[60,63]. Milibis and Aralen combined have not been successful[64]. Elsdon-Dew, et al, found fumagillin ineffective against the acute phase, although its direct amebicidal potential is high[65].

In the management of hepatic amebiasis, chlortetracycline or oxytetracycline alone are sometimes successful, but emetine or chloroquine are generally more reliable in South Africa as elsewhere[56,71].

Other Areas

Recent literature emanating from experiences in other areas of the world indicates an over-all picture quite similar to that already described; that is, there is great variation in prevalence reports as well as in manifestations and complications. These, insofar as related to the specific subject of this paper, will be briefly discussed in respect to the following regions: Near East, India, Far East, and Latin America.

Near East:—Although one source indicated that amebiasis was prevalent throughout the Near East[72], Anderson, Contopoulos, and Anderson found an over-all rate of about 12 per cent in a survey conducted at the American University of Beirut[73]. In Saudi Arabia, among Bedouin tribes, however, an estimated prevalence of 35 per cent was found among natives without intestinal complaints. The small race variety of *E. histolytica* is quite common (40 to 50 per cent), and appears to produce diarrhea. Acute dysentery and hepatitis are said to be more rare in the Arab East than in Egypt[73].

Immediate response to therapy is generally satisfactory and comparable to experience in North America[73,74].

Far East:—Amebiasis was a serious problem among the prisoners of war on the island of Koje, and 10 per cent of the hospital admissions for dysentery during May, June and July, 1951 had amebic infections; later the incidence increased. A severe form was very common. A large series of comparative chemotherapeutic trials indicated that oxytetracycline was the most effective agent in controlling the acute phase. Long term follow-ups for relapses could not be accomplished (Martin, et al[75]; Frye, Brooke, and Weinstein[76]).

Among United Nations troops, 10 per cent of 3,100 admissions to the medical wards of the Tokyo Army Hospital had diarrhea or dysentery. Many were chronic. In a study of 39 consecutive diarrhea patients, 69.2 per cent had amebiasis[77]. During an epidemic of amebiasis among Americans in a Tokyo apartment hotel, a relatively mild course was noted[78,79].

Among the Japanese population, Yokogawa, et al[80], reported that 10 per cent were positive.

In the Philippines, Tupas[81] stated that amebic dysentery and hepatic complications among children had increased greatly since World War II. This observation was unexplained although there is some feeling that more virulent strains were recently introduced.

In Indo-China, severe dysentery is very common, and the virulence of these "strains" is said to be much greater than those of North Africa[49]. Reports of clinical trials with various amebicides indicate a good response in acute cases to a variety of nonantibiotic agents, but cases of long duration generally required oxytetracycline[82].

India:—Amebiasis is said to constitute a more serious problem in India than bacillary dysentery[83,84]. In surveys of various outpatient clinical groups, prevalence rates over 50 per cent are found, and many asymptomatic infections occur. Acute disease is apparently more common in newcomers, the indigenous population usually presenting chronic complaints. All grades of clinical severity are seen, and many nonspecific systemic complaints are attributed to the infection[85].

In 2,000 cases of dysentery seen in British troops during World War II, approximately 1,000 were of amebic origin. The course was generally severe and 50 per cent of the acute intestinal cases had a mild amebic hepatitis during or following this phase; 3.9 per cent developed acute hepatitis and 2.8 per cent developed frank liver abscesses. Severe hemorrhage, amebomata, and peritonitis with and without perforation were seen in this series[86].

Extraintestinal amebiasis is frequently seen and clinical experience in India has been the source of considerable data concerning the efficacy of chloroquine[87-96].

Latin America:—In 44 surveys in 12 of these countries reported between 1938 and 1949, prevalence rates ranged from 1.2 per cent of 7,246 persons examined in Cuba by Calve Fonseca to 85 per cent of 271 clinic patients reported by Santos Zelima in Mexico. Rates estimated from combined survey data, as listed by Anderson, et al, ranged from 1.7 per cent in Ecuador (15,410 examined), to 30.3 per cent in Honduras (21,125 examined)[97]. Later surveys show similar variation: 24.29 per cent in school children of high altitude areas of Ecuador[98], 8.9 per cent in Venezuela among middle and high income groups[99], 5.93 per cent in Southern Chile[100]. All grades of severity were seen.

Anderson, et al[5], point out that the admission rate for amebiasis is higher in the John Gaston Hospital, Memphis, Tennessee than in the Hospital Santo Thomas in Panama City. In a later comparison of cases of amebiasis at the John Gaston Hospital in Memphis and the Hospital San Juan De Dios, San Jose, Costa Rica[101], both series of patients exhibited similar complaints. In the former, diarrhea was most common, together with abdominal pain, dysentery, constipation, and anorexia and recent weight loss in decreasing order of frequency. In the latter, diarrhea or dysentery was most common, accompanied by abdominal pain, severe malnutrition, and, less frequently, vomiting.

In a study of nondysenteric amebiasis among Navy personnel in Panama[102], Sapero observed 46 or 43.4 per cent of 106 apparently healthy men harboring *E. histolytica* to have complaints. A control group of 108 cases negative for intestinal protozoa revealed but 8, or 7.4 per cent to have complaints. Among the 46 men, abdominal pain was by far the most common complaint, 39 presenting this symptom. In many cases it was cramp-like and poorly localized; in others, it was dull and aching in nature and maximal in the lower quadrants. Only rarely was the pain severe. One-third of those questioned had bowel habits normal in every respect. Constipation as the sole complaint was about as frequent as diarrhea. The frequently mentioned symptom of alternating diarrhea and constipation occurred in only 8 cases. None of the cases had noted blood and mucus in their stools. Other complaints were nausea, vomiting, distention, "heartburn", headaches, nervousness, fatigability, and weight loss.

The proportion of patients acquiring recognized hepatic amebiasis is difficult to ascertain. Clark[103] found that approximately 50 per cent of autopsied

amebiasis victims had evidence of this complication to some degree, while Craig[104] reported liver abscess in only 5 per cent of 745 cases in 1944. Donoso[105] reviewed 10,910 autopsies in a Chilean hospital and found only 90 cases with amebic hepatitis and 22 with abscesses.

In Santiago, Chile, Badenez[106] found that 20.5 per cent of 159 unselected cases of acute appendicitis harbored *E. histolytica* in the appendix. Other recent clinical reports include pulmonary amebiasis[107], meningo-encephalitis[108], and amebic abscess of the foot[109].

Luis Carri reported symptoms of respiratory allergy in over 10 per cent of a series of 120 patients with amebiasis and indicates that improvement occurred after amebic therapy[110].

Summary

A review of the clinical literature of amebiasis from many temperate and tropical areas of the world has been presented with major emphasis on the manifestations, complications and therapeutic response. As with other cosmopolitan diseases, the severest forms of amebiasis do occur more frequently in areas of tropical location or culture, but amebiasis does constitute a significant problem in temperate climates as well. Throughout its world-wide distribution, the infection is characterized by protean manifestations. Although there may be strains with enhanced virulence in some areas (Indo-China and parts of Africa), it would appear that local factors, among them, diet, are of importance in determining the severity of the disease.

REFERENCES

1. McHardy, G.: Incidence of amebiasis. Gastroenterology (Editorial), **25**:616-617, 1953.
2. Elsdon-Dew, R.: The pathogenicity of *Endameba histolytica*. South African M. J., **27**:504-506, 1953.
3. Wright, W. H.: Public health status of amebiasis in the United States as revealed in available statistics. Am. J. Trop. Med., **30**:123, 1950.
4. Browne, D. C., McHardy, G. and Spellberg, M. A.: Statistical evaluation of amebiasis. Gastroenterology, **4**:154-163, 1945.
5. Anderson, H., et al: Incidence and control of amebiasis and other intestinal protozoa in a Memphis Hospital. Am. J. Trop. Med., **28**:373, 1948.
6. Browne, D. C., McHardy, G., and Edwards, E.: Amebiasis, A clinical evaluation. New Orleans Med. & Surg. J., **102**:475, 1950.
7. Dolkart, R. E.: Diagnosis and treatment of amebic dysentery. J. Am. Geriatrics Soc., **1**:477-485, 1953.
8. Alexander, F. D. and Meleney, H. E.: A study of diets in two rural communities in Tennessee in which amebiasis is prevalent. Am. J. Hyg., **22**:704, 1935.
9. Eyles, D. E., Jones, F. E. and Smith, C. S.: *Endameba histolytica* and other intestinal parasites in a rural west Tennessee community. Am. J. Trop. Med. & Hyg., **2**:173, 1953.
10. Faust, E. C.: Amebiasis in the New Orleans population as revealed by autopsy examinations of accident cases. Am. J. Trop. Med., **21**:35, 1941.
11. Conn, H. C., Feldman, P. H. and Taylor, A.: Amebiasis in veterans. J. Michigan M. Soc., **49**:174-181, 1950.

12. Lincicome, D. R., Thiede, W. H. and Carpenter, E.: An evaluation of the influence of World War II incidence of amebiasis. Am. J. Trop. Med., **30**:171, 1950.
13. Jacobs, L., Wallace, F. G. and Diamond, L. S.: Survey of intestinal parasites in soldiers being separated from Service. Bull. U. S. Army Med. Dept., **6**:259-262, 1946.
14. Palmer, E.: Military amebiasis. Am. J. Trop. Med., **26**:543-547, 1946.
15. Spellberg, M. A. and Zivin, S.: Amebiasis in veterans of World War II; special emphasis on extraintestinal complications including a case of amebic cerebellar abscess. Gastroenterology, **10**:452-473, 1948.
16. Brooke, M. M., Donaldson, A. W. and Brown, E.: An amebiasis survey in a Veterans Administration Hospital, Chamblee, Georgia, with comparison of technics. Am. J. Trop. Med. & Hyg., **3**:615-620, 1954.
17. Loeber, M. and D'Antoni, J. S.: Some recent experiences with amebiasis in children. New Orleans Med. & Surg. J., **100**:276-278, 1947.
18. Goldenberg, C., et al: Clinical Report: Amebiasis in infants under one year of age. J. Pediatrics. **40**:290-297, 1952.
19. Miller, M. J.: Studies on amebiasis: children passing cysts. Canad. M.A.J., **57**:373, 1947.
20. Miller, M. J. and Choquette, L. P. E.: Studies on amebiasis in Canada. Part I. Incidence of intestinal protozoal infections in two institutions in Canada. Canadian J. Res., Section E., Med. Sc., **25**:1-4, 1947.
21. Owen, W. B., et al: Protozoal infestations of American Indian children. J.A.M.A., **102**:913-915, 1934. (TDB **32**:188, 1935).
22. Albright, E. C. and Gordon, E. S.: Present status of the amebiasis problem. Arch. Int. Med., **79**:253-271, 1947.
23. Black, R. L., Terry, L. L. and Spicknall, C. G.: Fumagillin in the treatment of amebiasis. Gastroenterology, **27**:87, 1954.
24. Mayfield, M. F.: Amebiasis in rural Mississippi. Mississippi Doctor, **30**:311, 1953.
25. Tucker, W. H.: Treatment and prognosis in amebiasis. J.M.A. Alabama, **22**:231, 1953.
26. D'Antoni, J. S.: Conceptions and misconceptions in amebiasis. Am. J. Trop. Med. & Hyg., **1**:146-154, 1952.
27. Mackie, T. T., et al: Amebiasis in a civilian hospital and veterans patients in North Carolina. Southern M. J., **43**:313, 1950.
28. Tobie, J., Most, H., Reardon, L. and Bozicevich, J.: Laboratory results of efficacy of terramycin, aureomycin, and bacitracin in treatment of asymptomatic amebiasis. Am. J. Trop. Med., **31**:414, 1951.
29. Ivanhoe, G. L.: Studies on transmission of amebiasis in a children's home in New Orleans. Am. J. Trop. Med., **23**:401, 1943.
30. Kuitenen-Ekbaum, E.: Intestinal parasites in children in Toronto. Am. J. Dis. Child., **60**:518-525, 1940.
31. McVay, L. V., Laird, R. L. and Sprunt, D. H.: Treatment of amebiasis with Aureomycin. Southern M. J., **43**:308, 1950.
32. McHardy, G., et al: Fumagillin as an amebicide. Southern M. J., **46**:428, ff, 1953.
33. Most, H., et al: Treatment of amebiasis with bacitracin and other antibiotics. Am. J. Trop. Med., **30**:491, ff, 1950.
34. Radke, R. A.: Diagnosis and treatment of chronic amebiasis. Southern M. J., **45**:1027, ff, 1952.
35. Weiser, N. J., Spiotta, E. and Ekman, P.: Experiences in diagnosis and antibiotic treatment of amebiasis. Ann. Int. Med., **38**:1002, ff, 1953.
36. Levy, J. S. and Talley, R. W.: Balarsen (mercaptoarsenal) in amebiasis. Gastroenterology, **22**:588, 1952.
37. Rappaport, E. M., Rossien, A. X. and Rosenblum, L. A.: Arthritis due to intestinal amebiasis. Ann. Int. Med., **34**:1224, 1951
38. Klatskin, G.: Amebiasis of the liver: classification, diagnosis and treatment. Ann. Int. Med., **25**:601, 1946.
39. Ochsner, A. and DeBakey, M.: Amebic hepatitis and hepatic abscess. Surgery, **13**:460-493, (March), and 612 (April), 1934.
40. Berne, C. J.: Hepatic amebiasis—Diagnosis and treatment. Surg. Gynec. & Obst., **75**:235, 1942.
41. Warshawsky, H., et al: Hepatic complications of amebiasis. New England J. Med., **235**:678, 1946.

42. Heller, P., et al: Amebic hepatitis presenting as fever of unknown origin. New England J. Med., **249**:596-600, 1953.
43. Simmonds, E.: Complications of Amebiasis. Quar. Bull. Northwestern Univ. Med. School, **17**:25, 1943.
44. Bates, M.: Where winter never comes, Scribner, N. Y., 1952.
45. Simmonds, J. S., et al: Global epidemiology, V. 2, 1951. J. B. Lippincott Co., Philadelphia.
46. Lebon, J. F., et al: Les formes non-dysentériques de l'amibiase intestinale. Gaz. Med. de France, **57**:749, 1950 (Numero special).
47. Corcos, A.: Abcès du foie en Tunisie. Bull. Soc. Path. Exot., **46**:723-728, 1953. (abstracted in Trop. Dis. Bull. **51**:487, (May), 1954.)
48. Schneider, J. and Dupoux, R.: Traitement de l'amibiase intestinale par le bis-(p-arsonophenylamino) 1-2 ethane. Bull. Soc. Path. Exot. **46**:550-561, 1953. (Abstracted in Trop. Dis. Bull., **51**:60-61, 1954.)
49. Payet, M.: Amibiase hepatique. Gaz. Med. de France. **57**:763, 1950, (numero special).
50. Papers presented at the Fez, Morocco Conference. Maroc Med., **31**: No. 324, 1952.
51. Halawani, A., Abdallah, A. and El-Kordy, M. I.: Amebiasis in Egypt: Recent knowledge regarding its diagnosis, incidence and treatment with aureomycin. J. Royal Egyptian M. A., **34**:97-104, 1951.
52. El Mofty, A. and Moussa, A. H.: Clinical study of 900 cases of amebiasis in Egypt. Gaz. Kasr El Ainy Clin. Soc., **17**:1-66, 1951, (Spec. number).
53. El-Din, G. N.: Terramycin in amebic dysentery. J. Royal Egyptian M. A., **34**:150-152, 1951.
54. El-Din, G. N.: A preliminary report on "Wia" (a new bismuth-arsenical compound) in the treatment of amebic dysentery. J. Royal Egyptian M. A., **33**:518-520, 1950.
55. Killough, J. H., Magill, G. B. and Smith, R. C.: Treatment of amebiasis with Fumagillin. Science, **115**:71, 1952.
56. Rizzotti, G.: Contributo allo studio della varieta piccola dell'*Ent-amoeba histolytica*. Arch. Ital. Sci. Med. Trop. e Parassit., **33**:299-312, 1952 (Abstracted in Trop. Dis. Bull., **50**:512, 1953.)
57. Charmot, G. and Le Henand, F.: Dix observations d'amibiase hepatique traiteés par la terramycine. Bull. Med. de l'Afrique-Occidentale Francaise. **9**:259-264, 1952. (Abstracted in Trop. Dis. Bull., **51**:61, 1954.)
58. Charmot, G., Le Henand, F. and Giudicelli, P.: Note sur le traitement de l'amibiase intestinale aigue en A.O.F. per le bis (p-arsonophenylamino) 1-2 ethane. Med. Trop., Marseilles. **13**:207-209, 1953.
59. Anderson, G. V. W.: Surgical complications of amebiasis. East African M. J., **30**:467-473, 1953. (Abstracted in Trop. Dis. Bull., **51**:385-386, 1954).
60. Armstrong, T. G., Wilmot, A. J. and Elsdon-Dew, R.: Treatment of amebic dysentery in the Bantu. Trans. Royal Soc. Trop. Med & Hyg., **42**:597, 1949.
61. Elsdon-Dew, R.: Endemic fulminating amebic dysentery. Am. J. Trop. Med., **29**:337, 1949.
62. Elsdon-Dew, R. and Freedman, L.: Intestinal parasites in the Natal Bantu. South African J. Clin. Soc., **3**:59-65, 1952. (Abstracted in Trop. Dis. Bull., **50**:112, 1953.)
63. Armstrong, T. G.: Recent experiences in the treatment of amebiasis. South African M. J., **27**:42, 1953. (Abstracted in Trop. Dis. Bull., **50**:513, 1953.)
64. Wilmot, A. J., et al: Comparative values of amebicidal drugs. J. Trop. Med. & Hyg., **54**:161-165, 1951.
65. Elsdon-Dew, R., Wilmot, A. J. and Armstrong, T. G.: Fumagillin in amebiasis. Lancet, pp. 1180-1181, (Dec. 5), 1953.
66. Wilmot, A. J., et al: Aureomycin in amebic liver abscess. Am. J. Trop. Med. & Hyg., **1**:429-435, 1952.
67. Jelliffe, D. B.: Amebic hepatitis treated with chloroquine. J. Trop. Med. & Hyg., **54**:114, 1951.
68. Patel, J. C.: Chloroquine in the treatment of amebic liver abscess. Brit. M. J., p. 811, (April 11), 1953.
69. Wilkinson, J.: Toxicity of chloroquine in hepatic amebiasis in Africans. East African M. J., **30**:403-415, 1953. [Abstracted in Trop. Dis. Bull., **51**:487, (May), 1954.]
70. Manson-Bahr, P.: Chloroquine in amebic abscess. J. Trop. Med. & Hyg., **52**:91, 1949.

71. Murgatroyd, F. and Kent: Chloroquine in Amebic abscess. Trans. Royal Soc. Trop. Med. & Hyg., **42**:15, 1948.
72. Simmonds, J. S., et al: Global epidemiology, **3**:195, Lippincott, Philadelphia.
73. Anderson, H., Contopoulos, A. N. and Anderson, J. Van D.: Current status and therapy of amebiasis in the Arab East. J. Royal Egyptian M. A., **35**:4, 227-238, 1952.
74. Berberian, A. D., et al: Effectiveness of bismuthoxy-p-n-glycolylarsanilate (Milibis) in the treatment of intestinal amebiasis. Am. J. Trop. Med., **30**:613, (Sept.), 1950.
75. Martin, G. A., Garfinkel, B. T., Brooke, M., Weinstein, P. and Frye, W.: Comparative efficacy of amebicides and antibiotics in acute amebic dysentery. J.A.M.A., **151**:1055, (Mar. 28), 1953.
76. Frye, W., Brooke, M. and Weinstein, P.: Antibiotics in the treatment of acute amebic dysentery. Ann. N. Y. Acad. Sc., **55**:1104-1113, (Dec.), 1952.
77. Kraus, H.: Chronic diarrhea: Clinical and laboratory study of 39 cases. U. S. Armed Forces M. J., **4**:1584, (Nov.), 1953.
78. Ritchie, L. S. and Davis, C.: Parasitological findings and epidemiological aspects of epidemic amebiasis occurring in the Mantetsu Apartment building, Tokyo. Am. J. Trop. Med., **28**:803, 1948.
79. Davis, C. and Ritchie, L. S.: Clinical manifestations and treatment of epidemic amebiasis occurring in occupants of the Mantetsu Apartment building, Tokyo. Am. J. Trop. Med., **28**:817, 1948.
80. Yokogawa, M., et al: Mass treatment of *E. histolytica* carriers. U. S. Armed Forces M. J., **4**:1776, (Dec.), 1953.
81. Tupas, A. V., et al: Liver complications of amebiasis in children. J. Philippine M. A., **27**:397, (June), 1951.
82. Collomb, H. and Sankale, M.: La therapeutique de l'amibiase intestinale par le bis-(p-arsonophenyl-amino)-1-2, ethane, sel sodique. Bull. Soc. Path. Exot., **46**:749-764, (May), 1953. [Abstracted in Trop. Dis. Bull., **51**:488, (May), 1954].
83. Simmonds, J. S., et al: Global epidemiology, V. 1, 1944, Lippincott, Philadelphia.
84. Anderson, H., Bostick, W. L. and Johnstone, H. G.: Amebiasis: Pathology, diagnosis and chemotherapy. Charles C. Thomas, Springfield, Ill., 1953.
85. Mahajan, K. R.: Chronic intestinal amebiasis. J. Indian M. A., **22**:490-492, (Sept.), 1952. (Abstracted in Trop. Dis. Bull., **51**:60, 1954.)
86. Payne, A. M. M.: Amebic dysentery in Eastern India. Lancet, **1**:206, 1945.
87. Chakravarti, A.: Intestinal ameboma: Three cases treated with chloroquine. J. Indian M. A., **23**:70-72, (Nov.), 1953. [Abstracted in Trop. Dis. Bull., **51**:268, (Mar.), 1954].
88. Chakravarti, A.: Pulmonary amebiasis (with particular reference to chloroquine therapy). J. Indian M. A., **22**:418-422, (July), 1953, [Abstracted in Trop. Dis. Bull., **50**:1044, (Nov.), 1953].
89. Chakravarti, A.: Pulmonary amebiasis. J. Indian M. A., **21**:320, (June), 1952.
90. Subramaniam, R.: Chloroquine in extraintestinal amebiasis. Indian Med. Gaz., **87**:295, (July), 1952.
91. De, S. N., and Sengupta, K. P.: Amebic appendix and its perforation. J. Indian M. A., **21**:242, (Mar.), 1952.
92. Sharma, L. R., et al: Chloroquine in the treatment of amebic abscess. Indian Med. Gaz., **86**:6, 1951.
93. Subramaniam, R.: Chloroquine in amebic abscess. Antiseptic, **48**:173, 1951.
94. Harinsuta, C.: Comparison of chloroquine and emetine in the treatment of amebic liver abscess. Indian Med. Gaz., **86**:137, (Apr.), 1951.
95. Harinsuta, C.: Chloroquine in the treatment of amebic abscess. Indian Med. Gaz., **85**:37, 1950.
96. Mukherjee, S. K.: Pulmonary amebiasis. Indian Med. Gaz., **84**:250, 1949.
97. Anderson, H., Bostick, W. L. and Johnstone, H. G.: op. cit., table II, p. 19.
98. Leon, L. A.: Climate and tropical diseases in upper levels of Ecuador. Abstracted: Trop. Dis. Bull. **46**:573, (June), 1949.
99. Vegas, J. S.: Evaluation of the newer amebicides. J.A.M.A., **151**:1059, (Mar. 28), 1953.
100. Neghme, A., et al: Survey of intestinal parasites in southern Chile. Abstracted in Trop. Dis. Bull., **50**:512, (June), 1953.
101. Anderson, H., Bostick, W. L., and Johnstone, H. G.: op. cit., Table XV, p. 201.

102. Sapero, J. J.: Amebiasis: Clinical studies of nondysenteric intestinal amebiasis. Am. J. Trop. Med., **19**:497, 1939.
103. Clark, H. C.: Amebiasis: Distribution of lesions and complications found at postmortem examination. Am. J. Trop. Med., **5**:157, 1925.
104. Craig, C. F.: Etiology, Diagnosis and treatment of amebiasis. p. 332, 1944. (Williams & Wilkins, Baltimore).
105. Donoso, I., et al: Pathologic findings as to causes of death in amebiasis. Rev. Med. Chile, **80**:413, (July), 1952. [Abstracted in Trop. Dis. Bull., **50**:512, (June), 1953].
106. Badinez, S., et al: *E. histolytica* in appendices removed at emergency operations in Santiago, Chile. Bol. Inform. Parasit. Chilenas., **7**:36, (July-Sept.), 1952. [Abstracted in Trop. Dis. Bull., **50**:117, (Feb.), 1953].
107. Rodriguez, C. and Adrianza, H. M.: Pleuro-pulmonary complications of amebiasis. Arch. Venezolanos de Patol. Trop. y Parasit. Med., **1**:89, (Jan.), 1950. [Abstracted in Trop. Dis. Bull., **50**:217, (Mar.), 1953].
108. Miguel, H.: Meningo-encephalitis caused by *E. histolytica*. Arch. Med. Panamenos., **1**:149, (Apr.-May-June), 1952.
109. Nowicki, E. L.: Amebic abscess of the foot. J.A.M.A., **150**:813, (Oct. 25), 1952 (correspondence).
110. Luis Carri, E.: Intestinal amebiasis and respiratory allergy. Abstracted in Trop. Dis. Bull., **46**:145, (Feb.), 1949.

CLINICAL CONSIDERATIONS OF AMEBIASIS*

LUTHER L. TERRY, M.D.†

Bethesda, Md.

Studies on the incidence of amebiasis throughout the world indicate that the disease is found wherever it is suspected and looked for. It seems quite clear that it is more frequent in warm climates and that there is a definite relationship between the incidence of amebiasis and poor environmental hygiene. Nevertheless, it is encountered sufficiently frequently in any area that all physicians should be alert to the possibility. Since amebiasis can be manifest clinically in such diverse fashions it is especially easy to overlook many types of the disease and such a lapse on the part of the physician may be tragic for the patient.

The recognition of amebiasis in a patient with acute bloody dysentery is not particularly difficult. Despite the fact that in occasional instances the amebae are difficult to find in the stool of patients with acute amebic dysentery, these cases are usually suspected early and diagnosed promtply. This is, however, a relatively rare type of the disease in the Western Hemisphere. Accordingly, I would like to direct attention to certain clinical considerations of amebiasis which illustrate some of the more serious types of the disease which may be confused with other entities. It is these types of amebiasis which tax the skill of the diagnostician and so greatly improve the patient's prognosis if they are promptly recognized.

Chronic Intestinal Amebiasis

Nondysenteric amebiasis is the most common clinical form of the disease in this country. In contrast with acute dysentery the symptoms in chronic cases begin insidiously and are frequently variable. Diarrhea may develop very late in the course of the disease. Constipation may be a more constant feature. It is not uncommon to find diarrhea alternating with constipation or periods of apparently normal bowel movements. Even when diarrhea is present the stools rarely contain gross blood but may contain considerable mucus. Aching abdominal pain, especially in the lower quadrants is a common symptom. The abdominal distress is frequently associated with flatulence and is often worse during periods of greater flatulence. A poor appetite and considerable weight loss are frequently encountered. In some instances the symptoms are fairly constant, while in others they wax and wane. Some patients experience alternating periods of ill health and temporary recovery. As the disease is established in its chronic

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

From the Medical Service, USPHS Hospital, Baltimore, Maryland and the National Institutes of Health, Public Health Service, Department of Health, Education and Welfare, Bethesda, Maryland.

†Formerly Chief of Medical Service, USPHS Hospital, Baltimore, Maryland.

form, however, irritability of the colon is probably the most common clinical syndrome.

The physical signs of chronic intestinal amebiasis are equally variable and ill-defined. In cases where there is extensive invasion of the cecum or other areas of the colon, masses may be palpated. More frequently one will find that the patient is tender over all or most of the palpable course of the large bowel. In some instances the abdomen may be completely normal on physical examination.

Since the history and physical findings are so variable in chronic amebiasis it is obvious that in most instances they will serve only to make one suspicious of the disease. For this reason it is especially important for one to recognize the value of other diagnostic methods. The most important of these examinations is a careful sigmoidoscopic study. Fully half the cases of intestinal amebiasis will show some lesions in the sigmoid colon and rectum. Such lesions may vary from small, relatively clean superficial ulcers to large, undermined ulcers covered with necrotic exudate. All lesions, regardless of size or form, should be carefully scraped with a dull curette and the material examined immediately. Occasionally, one will encounter polypoid, granulomatous lesions which may be biopsied but this is unusual in our experience. The diagnostic study of second importance is careful stool examination and culture by trained personnel. Finally, a certain number of these cases can be diagnosed with barium studies of the colon. Though this technic may supply strong presumptive evidence of amebiasis, the findings are easily confused with other lesions of the colon, especially malignancy. In such instances the final diagnosis must rest upon the presence or absence of ameba in the stool or even upon the response of the lesion to amebicidal therapy. It is difficult to sit by and wait for the response of a lesion of the colon to chemotherapy when one realizes that valuable time may be lost if there is a malignancy present. On the other hand, it is clearly the better part of valor to wait in instances where the suspicion is sufficiently strong since one may avoid a needless mutilating operation and since complications of such surgery in amebiasis are so frequent and so severe.

Amebic Granuloma (Ameboma)

Repeated invasion of the wall of the colon by *E. histolytica* may result in the formation of a granulomatous mass which may be detected on physical examination, or viewed on sigmoidoscopic examination, or demonstrated on barium enema. Such lesions so closely resemble carcinoma of the colon that they often present serious diagnostic and therapeutic problems. One is faced with the realization that such a mass may be a malignancy even though ameba are demonstrated in the stool. It is a fortunate circumstance when such lesions are located within reach of the sigmoidoscope in order that a biopsy may be taken and the diagnosis can be made more quickly. Discrete biopsies can be taken with relative impunity and are practically always successful in differentiating between these two possibilities. When the lesion is beyond the reach of

the sigmoidoscope the problem is much more difficult. As mentioned above, however, in instances where the probability of amebiasis is sufficiently great, one is clearly obligated to a course of amebicidal therapy as the patient is followed closely.

Amebic Hepatitis and Hepatic Abscess

The manifestations and course of amebic involvement of the liver have been repeatedly described and are well known to most physicians. It is a repeated source of surprise, however, to see these cases go for long periods of time without amebiasis having been suspected. If the lesion has progressed to the stage of a discrete abscess with the characteristic deformity of the right diaphragm it is not commonly mistaken. On the other hand, if there is diffuse liver involvement, or a localized hepatic lesion without distortion of the diaphragms, or if the process has already ruptured into the pleura the degree of recognition is considerably lessened. Our experience at the U. S. Public Health Service Hospital in Baltimore has been a most interesting one and serves to illustrate some interesting aspects of amebic involvement of the liver.

All three cases of amebic abscess of the liver with rupture into the pleura who had been studied by other physicians prior to entry to the hospital were referred to the Tumor Clinic because malignancy of the lung and pleura was suspected most strongly. This was true in spite of the fact that their ages were 19, 25 and 28 years. The suspicion in each instance was based primarily on obtaining bloody fluid on thoracenthesis. In each instance, the viscid nature of the fluid obtained on tap, the absence of tumor cells on smear of the fluid, and the evidence of an infectious process as shown by a high white blood cell count, fever, etc., resulted in a prompt suspicion of amebiasis in our hospital. I mention this experience only to suggest the fact that certain features are present on investigation to make one suspicious of amebiasis if one is alert to the possibility. It is not uncommon that initial x-ray of the chest will reveal complete or almost complete obliteration of the lung field on the right side. Since these patients commonly give no history suggestive of amebiasis, the natural tendency is to think first of empyema or a tuberculous pleural effusion. This is especially true if the patient is young. In older patients the possibility of malignancy receives more serious consideration. The demonstration of a very viscid fluid on diagnostic thoracenthesis should, however, make one immediately alert to the possibility of an amebic process. The presence of fresh or older blood-stained fluid should make one even more suspicious. If the fluid is chocolate brown or bile-tinged the finding is almost pathognomonic. Frequently, after fluid has been removed one can demonstrate the deformity of the diaphragm especially if the film is heavily exposed.

Other cases of amebic liver abscess have at first been thought to be cases of pneumonia. Sometimes the clinical course is relatively benign until rupture occurs. Since the patient presents himself with chest pain and a history of acute onset, the suspicion seems reasonable. The case may be further confused by x-ray

findings in the right lower lung field which are consistent with a primary pneumonitis. In these instances the correct diagnosis is first suspected as a result of careful study of the x-rays, especially if the lateral views or heavily exposed P.A. films are available. We have made it a rule to consider the possibility of amebiasis in any chest lesion in which the area of the right diaphragm is obscured. It is true that further examination with special x-ray views will often dispel the possibility of amebiasis but the incidence of amebic hepatitis is great enough to justify this general rule.

In summary, it is well worth repeating that "amebiasis is found where it is suspected and looked for." There is no simple answer to the problem of diagnosis. There are, however, a few guide lines which we have found helpful and which may be useful to others.

1. Since chronic intestinal amebiasis is the most frequent form of the disease in this country, it should be suspected in all cases with vague abdominal symptoms unless other diseases have been clearly proven.

2. The sigmoidoscope is an extremely valuable diagnostic instrument in intestinal amebiasis. The best diagnostic material can be obtained for direct examination and culture by using a dull curette when ulcers are found. If granulomatous lesions are present, biopsy is a safe and effective diagnostic procedure.

3. Barium x-ray examination of the colon is frequently helpful in those cases in which no lesions are found on sigmoidoscopy. This is true either with localized lesions such as amebomas or with more diffuse lesions.

4. Amebic hepatitis should be suspected in any instance where a large tender liver is found. The suspicion is increasingly greater if there is slight or no jaundice and if the liver function studies are not characteristic of diffuse impairment of liver function.

5. Liver abscess should be considered in any case where x-ray examination revealed an abnormal contour of the right diaphragm.

6. Rupture of an amebic abscess of the liver into the chest should be suspected in every chest lesion involving the right lower lung unless and until a normal contour of the right diaphragm has been demonstrated.

7. A viscid pleural fluid, with or without blood, is suspicious of an amebic process. This is especially true of the younger age group.

8. One should not rely upon the presence of a positive stool to confirm the diagnosis of extraintestinal amebiasis.

9. The complement fixation test is of great value in the diagnosis of extraintestinal amebiasis. It has essentially no value in the diagnosis of intestinal disease.

10. Hematogenous lesions of amebiasis are extremely rare and most often occur in cases with fulminating intestinal disease or involvement of the lung.

PARASITOLOGICAL CONSIDERATIONS RELATIVE TO THE DIAGNOSIS OF AMEBIASIS*

JOHN E. TOBIE, Ph.D.†

Bethesda, Md.

The definitive diagnosis of amebiasis rests upon the morphological identification of the causative protozoan, *Endameba histolytica*. At a casual glance one might think that it is easy simply to find the organism, identify it and thereby establish the diagnosis. In practice it is not all that simple since often it is most difficult to detect the amebae and once they have been detected, it may be quite difficult to differentiate them from the other harmless intestinal protozoa. The identification of the protozoa found in the human intestine is based on detailed morphology and requires that the observer first be an excellent microscopist and secondly an individual highly trained in the minute structures of the various protozoan parasites. The latter is most pertinent since the average laboratory technician ordinarily has very limited training in the identification of the amebae and performs stool examinations only occasionally. There are certain laboratories throughout the United States that have highly specialized diagnosticians but these are in the minority. It is the type of study that requires much training and day to day contact and even so, diagnostic errors are still made. For proper evaluation of the case the clinician should be fully aware of the difficulties encountered in the accurate identification and differentiation of the amebae.

Five species of amebae are found in the intestine of man: *Endameba histolytica, Endameba coli, Endolimax nana, Iodameba butschlii* and *Dientameba fragilis*. Of these only one, *E. histolytica*, has been shown definitely to be pathogenic. From the standpoint of the laboratory diagnostician, therefore, it is necessary to differentiate *E. histolytica* from the other harmless commensals.

There are two stages in its life cycle, the trophozoite and the cyst. The active trophozoite stage is usually found in dysenteric, diarrheic or semiformed stools while the quiescent cyst stage is found in semiformed or formed stools. When the trophozoite of *E. histolytica* is observed in a case of frank dysentery it is most characteristic and few errors in diagnosis should be experienced. Diagnosis in this case is based principally upon the actively progressive and directional motility, the clear glass-like pseudopodia and red blood cell inclusions. It must be remembered, however, that the vast majority of cases of amebiasis in the United States do not exhibit dysenteric symptoms and that the trophozoites from these patients do not have the characteristic red blood cell inclusions.

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

†Laboratory of Tropical Diseases, U. S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Microbiological Institute, Bethesda, Maryland.

E. histolytica trophozoites, as seen in fresh preparations, which contain no red blood corpuscle inclusions are often extremely difficult to differentiate from the other intestinal amebae. As a consequence, it is becoming more and more the opinion of experienced laboratory workers that only tentative diagnoses should be made on trophozoites and that more accurate information can be obtained from the examination and identification of the cysts.

The most characteristic and diagnostic structure of a cyst of *E. histolytica* is the nucleus. The mature cyst has four nuclei in an organism which only averages 7 to 15 microns in diameter. It should not be difficult to visualize the minute size of the individual nucleus and the extremely minute structures contained within the nucleus. In many cysts it is most difficult to discern all of the details so it is essential that many organisms be observed before a scientific diagnosis can be established. Generally, the nucleus of *E. histolytica* has small discrete dots of chromatin arranged on the inner surface of the nuclear membrane and a minute centrally placed karyosome. Although this is usually the case, there are often structural variations, so much so that it may somewhat resemble the heavier peripheral chromatin and eccentric karyosome of the nonpathogenic ameba, *E. coli*. Without going into further structural differences it is quite evident that even in the identification of the cyst of *E. histolytica*, considerable difficulty is encountered and extreme caution must be exercised before a definitive diagnosis is made.

Another important consideration in the parasitological diagnosis of amebiasis is concerned with the technic that should be employed for detecting the organism. If the stool specimen under examination is of a dysenteric, diarrheic or semi-formed nature, then a direct unstained smear should be prepared and a search made for the motile trophozoites. Such an examination should be performed on a freshly passed fecal specimen because at certain times the amebae remain alive for only a short period of time after being voided. Some workers prefer permanent hematoxylin-stained smears. Although such preparations are of definite value, the time consumed makes the technic somewhat impractical for most diagnostic laboratories. In the search for cysts of the amebae in semi-formed or formed stools, one of the most reliable technics is the iodine-stained direct smear. With stools of this character, however, a concentration method, such as the zinc sulfate centrifugal flotation technic, should also be employed. Such a method has the distinct advantage of separating the cysts from the fecal material, thus effecting a tremendous concentration of the organism. Large numbers of cysts, essentially free of fecal debris and obscuring bacteria, are then available for a more rapid and accurate diagnosis. The mircoscopist familiar with the iodine-stained direct smear and the iodine-stained zinc sulfate preparation finds the latter much more satisfactory. In a study of the efficiency of stool diagnostic technics performed by a group of us from the National Institutes of Health[1], it was shown that for cysts of *E. histolytica* the iodine-stained direct smear technic was only 27 per cent efficient while the zinc sulfate technic

was 59 per cent efficient. The chances of detecting the amebic cysts and establishing a diagnosis are thus greatly increased when a concentration method is used.

Whenever practical, repeated stool examinations should be requested providing there is ample clinical evidence suggesting amebiasis. As a part of the above study[1], 28 persons known to harbor *E. histolytica* were examined repeatedly by the zinc sulfate technic. Of the 28 infected persons, 71 per cent were diagnosed on the first examination, 82 per cent through the second, 86 per cent through the third, 96 per cent through the fourth and 100 per cent through the fifth examination. Thus, it required five stool examinations on these individuals before we could find all of them positive. It has been well established that the numbers of amebae present in the feces of an infected person may vary from day to day or week to week. At times large numbers of organisms may be present and perhaps the next day or next week no organisms can be detected. The advisability of accepting a single negative report is thus questioned.

A few laboratories employ cultural technics as aids in the diagnosis of amebiasis but as a general rule stool examinations have proven more satisfactory. The media utilized in the cultivation of *E. histolytica* are not easily prepared and much variation is encountered in establishing cultures. Once a culture is established the diagnostician is confronted with differentiating the trophozoites of the various species of amebae.

The parasitological diagnosis of amebic liver abscess and lung abscess is even more difficult than that of intestinal amebiasis. Although such complications originate from a previous intestinal infection, at the particular time it may be impossible to detect the amebae in the stool. Direct examination of liver aspirate or sputum has proven only mildly effective. In most cases of liver and lung abscess, the clinician must rely upon serological evidence, x-rays and clinical symptomatology.

REFERENCE

1. Tobie, John E., Reardon, Lucy V., Bozicevich, John, Shih, Bao-Chih, Mantel, Nathan and Thomas, Elizabeth H. The efficiency of the zinc sulfate technic in the detection of intestinal protozoa by successive stool examinations. Am. J. Trop. Med. **31**:552-560, 1951.

SEROLOGICAL CONSIDERATIONS RELATIVE TO THE DIAGNOSIS OF AMEBIASIS*

JOHN BOZICEVICH, M.S.†

Bethesda, Md.

It is generally recognized today that amebiasis is a complicated disease. At one time it was considered mainly as an intestinal involvement. During the past 20 years, however, the development of serological procedures has resulted in the diagnosis of more and more extraintestinal cases of amebiasis. These have included abscesses of the liver, lung and brain. Since extraintestinal infections tend to produce protean symptoms, and since stool examinations fail to reveal any evidence of amebic infection in a large percentage of such cases, serological tests furnish one of the best methods of diagnosis.

Terry and Bozicevich[1] reported 13 cases of hepatic involvement, 10 of which gave positive complement fixation reactions when first tested: or an efficiency of 77 per cent. The 3 individuals whose sera gave negative complement fixation tests were bled again the following week and 2 of the sera were positive. The efficiency of the test was thus raised to 91 per cent. It can be seen, therefore, that falsely negative results can be expected; varying from 9 to 13 per cent. Falsely positive reactions were not encountered in the above series.

False positives were found, however, in 8 to 10 per cent of several hundred sera submitted to us through the courtesy of Drs. Gibb, Perry and Sexton. These sera were drawn from individuals with gastrointestinal symptoms whose stools were judged negative for amebae.

False negatives also occur frequently in intestinal amebiasis. The complement fixation test is not as satisfactory as in the diagnosis of intestinal amebiasis, although it compares quite favorably to the direct smear method of stool examination. Tobie et al[2] reported the results of a survey of a mental institution at which stool examinations were made on 684 specimens from 234 individuals. A single direct smear proved 27 per cent efficient. The complement fixation test conducted on sera from these patients was 25 per cent efficient (unpublished data). The zinc sulfate flotation method of stool examination, however, gave an efficiency of 64 per cent; far greater than that of the other two methods.

In a second stool survey for *Endameba histolytica* infection conducted by Commander Ruebush at the Naval Medical Center, 25 of 429 persons were

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.

†Laboratory of Tropical Diseases, U. S. Department of Health, Education and Welfare, Public Health Service, National Institutes of Health, National Microbiological Institute, Bethesda, Maryland.

found to be carriers of amebae. The stools of 16 of the 25 contained small race *E. histolytica*. All 16 gave negative complement fixation tests with antigens prepared from large and small race amebae[3]. The remaining 9 had large race and only 5 of these gave positive complement fixation tests with an antigen prepared from large race amebae. A small race antigen gave negative results.

Commander Ruebush's survey disclosed a great many individuals who were infected with protozoans other than *E. histolytica*. The complement fixation test on the sera obtained from these individuals did not give falsely positive reactions. From our experience, therefore, it appears that *E. histolytica* antigen will not detect infections with protozoans other than *E. histolytica*.

There are indications that strain differences in *E. histolytica* do exist. For example, of a total of 2,412 serum samples examined by 2 antigens prepared from strains "103" and "104", 699 gave positive complement fixation results with both antigens. One hundred and sixty-eight were positive with "103" antigen but negative with "104". Contrariwise, 101 gave negative results with "103" antigen but were positive with "104". More recently our "F22" antigen gave positive complement fixation tests on proven cases in which the other 2 antigens gave negative results. Thus, it appears that a polyvalent antigen will be necessary for the diagnosis of amebiasis by serological methods.

We have no definite knowledge on the persistence or evanescence of antibody titers. To date we have evidence that in some cases the complement fixation test may yield negative results from 2 to 4 weeks after successful therapy. Contrariwise, we have seen complement fixation tests remain positive up to 3 years following successful therapy. In most instances, however, the antibody titers drop following therapy. In instances of delayed serological response the patient should be followed closely for a longer period of time than those in which the serological titer drops relatively fast after therapy.

The current complement fixation antigen grown with a single species of micro-organism in the presence of rice starch has a definite handicap. The metabolic products from micro-organisms and the rice starch tend to make the antigen anticomplementary. During the processing of the antigen the rice starch granules are broken up and a great deal of the antigen is adsorbed on the starch particles. Elution of antigen from the starch has not proven successful. Shaffer, et al[4] have shown that *E. histolytica* can be grown with tissue cells without accompanying micro-organisms. Rees and Reardon[5] have taken advantage of this discovery and are growing the amebae in a dialysate- and heat-treated media containing chick mince. Harvests of amebae grown by the latter method have given good antigenicity and the antigen is not anticomplementary. The mince apparently does not adsorb as much antigen as starch granules. Greater quantities of the new antigen are needed before thorough study of the specificity and sensitivity can be conducted.

REFERENCES

1. Terry, Luther L. and Bozicevich, John: The importance of the complement fixation test in amebic hepatitis and liver abscess. Southern M. J., **41**:691-702, 1948.
2. Tobie, John E., Reardon, Lucy V., Bozicevich, John, Shih, Bao-Chih, Mantel, Nathan and Thomas, Elizabeth H.: The efficiency of the zinc sulfate technic in the detection of intestinal protozoa by successive stool examinations. Am. J. Trop. Med. **31**:552-560, 1951.
3. Bozicevich, John: Discussion (Amebiasis panel). Am. J. Trop. Med. **30**:154-157, 1950.
4. Shaffer, V. G., Sienkiewicz, H. S. and Washington, V. E.: The propagation of *Endameba histolytica* in tissue-bearing culture without accompanying bacteria or other micro-organisms. Am. J. Hyg. **57**:366-379, 1953.
5. Rees, Charles W. and Reardon, Lucy V.: Experiments on the growth of *Endameba histolytica* in dialysate- and heat-treated media. Am. J. Trop. Med. and Hyg. Abst. to be presented 1954 annual meeting.

EXPERIENCE IN THE TREATMENT OF AMEBIASIS AT THE USPHS HOSPITAL, BALTIMORE*

LUTHER L. TERRY, M.D.†
Bethesda, Md.
and
CHARLES G. SPICKNALL, M.D.‡
Baltimore, Md.

At this time the problem of treatment of amebiasis is a confusing issue. We have available massive data of experience with the older amebicidal preparations such as iodides, arsenicals and emetine. More recently chloroquine and a large number of antibiotics have been introduced and used fairly extensively. From all this experience it seems very likely that no one of these agents is completely satisfactory when used alone in the treatment of the various types of amebiasis. Nevertheless, many of these agents have been shown to possess potent amebicidal activity and to give a high incidence of effectiveness when used in certain groups of cases. Therefore, the recent trend in the treatment of amebiasis has been towards the use of various combinations of therapeutic agents. As a result there is little or no unanimity of opinion relative to the best therapeutic regimen for the various types of amebiasis.

Over the past few years we have had the opportunity to treat several hundred cases of amebiasis as the USPHS Hospital in Baltimore. The vast majority of these cases received rather conventional therapy using iodides, arsenicals, emetine, and, more recently, chloroquine. In addition, we have treated a group of carefully studied cases with one of the new antibiotics, fumagillin. These cases were carefully observed and studied both as to the effectiveness of the therapeutic agent and to its toxicity. On the basis of this experience, combined with information published in medical literature, we would like to review briefly some of the aspects of the treatment of amebiasis. It is impossible to be complete in such a brief review but it is hoped that the salient points will be covered.

Intestinal Amebiasis

It has long been established that emetine is a very effective agent in the symptomatic treatment of acute amebic dysentery. Commonly, there is a dramatic response within hours to a few days to the daily subcutaneous administration

---

*Read before the First Annual Convention of the American College of Gastroenterology, Washington, D. C., 25, 26, 27 October 1954.
From the Medical Service, USPHS Hospital, Baltimore, Maryland.
†Former Chief of Medical Service, USPHS Hospital, Baltimore, Maryland; now associated with the National Heart Institute, Bethesda, Md.
‡Chief of the Medical Service, USPHS Hospital, Baltimore, Md.

of 65 mg. of emetine hydrochloride. It is well recognized that emetine does not accomplish a high cure-rate if used alone, and a large percentage of the cases will relapse. In addition, emetine is a toxic drug if given for many days at this dosage level. Since there are possibly other drugs which are equally effective in acute amebic dysentery and since emetine is potentially toxic, the tendency is to use emetine less frequently in intestinal amebiasis. We have continued to use it occasionally in acute amebic dysentery but not for periods of more than 5 or 6 days and then, only in combination with other amebicidal agents. On this regimen we have not encountered significant toxicity and the drug has appeared quite effective in checking the profuse diarrhea associated with this type of disease. It seems quite generally agreed that emetine does not have any particular value in other types of intestinal involvement.

The vast majority of cases of intestinal amebiasis encountered in this country are less tempestuous and are classified as chronic cases or carriers. In these cases the symptomatic manifestations are often mild or negligible and one is interested in a therapeutic regimen which is less toxic and more effective in eradicating the infection. For many years our routine therapy consisted of carbarsone (250 mg. 2 or 3 times daily for 10 days) combined with or followed by Diodoquin (1.0 to 2.0 grams daily for 20 days). This regimen was fairly satisfactory and resulted in eradication of the infection in a fairly high percentage of the cases. It was, however, frequently not well tolerated by the patient and most of us have been anxious for a more satisfactory treatment schedule.

As early as 1945 Hargreaves[1] reported on the use of an antibiotic in the treatment of amebiasis. He treated 57 patients with penicillin and noted some symptomatic improvement. *E. histolytica*, trophozoites, however, continued to be found in the stools and the improvement was attributed to the effect of penicillin on the secondary bacterial infection. In 1950 McVay, Laird and Sprunt[2] and Armstrong, Wilmot and Elsdon-Dew[3] reported favorably on the use of chlortetracycline. Most and van Ansendelft[4] used oxytetracycline in the treatment of 54 patients with amebiasis. Though the majority of these were asymptomatic or only slightly ill, there were 5 patients with severe disease. The severe cases responded "as well as with emetine" and the stools of all patients became negative following therapy. Shortly thereafter Tobie et al[5] reported on the treatment of a large group of asymptomatic cases in a mental institution using oxytetracycline, chlortetracycline and Bacitracin. Oxytetracycline was 100 per cent effective in eliminating the organism on the basis of a 6-month follow-up; chlortetracycline was 60 per cent effective and Bacitracin was only 28 per cent effective after 2½ months. Killough and Magill[6] also reported favorably on the use of oxytetracycline in 7 cases of acute amebic dysentery. All patients showed marked improvement of symptoms and the disappearance of ameba from the stools within 8 days. One patient, however, developed an hepatic abscess during oxytetracycline therapy.

In 1953 Martin et al[7] reported on the comparative efficacy of amebicides and antibiotics used alone and in combination in 538 cases treated in the Far East. The best initial response and the lowest relapse rate was observed in those cases treated with oxytetracycline alone and in combination with (1) emetine, (2) carbarsone, (3) chiniofon, (4) chloroquine diphosphate, (5) bismuth glycolyarsinalate and chloroquine, and the combination of chloretetracycline and chloroquine diphosphate. They, too reported one instance in which a patient under treatment with oxytetracycline developed evidence of liver involvement which subsided following therapy with chloroquine. They felt that their findings suggested an advantage of combined therapy.

One of the promising new antibiotics recently introduced in the treatment of amebiasis is fumagillin. Killough and co-workers[8] first reported favorably on its efficacy in intestinal infection in man. McHardy, Bechtol, Welch and Browne[9] also found good results in 134 patients. We[10] have had the opportunity to study fumagillin in 30 cases of intestinal amebiasis. Seventeen asymptomatic carriers and 13 patients with symptoms attributable to amebiasis were treated with 10 milligrams of fumagillin 3 times daily for 14 days. On this regimen all stools were negative immediately after treatment and at the end of 6 weeks or longer 87 per cent of those followed remained negative. Most of the patients were hospitalized during treatment, and careful studies were performed in an effort to detect any toxic effect upon the liver, kidneys or hemopoetic system. In no instance was there evidence of serious toxicity. Interestingly enough, one of our patients with a cecal lesion and a positive stool responded to fumagillin and the lesion in the cecum disappeared; however, the patient returned in one month with an amebic granuloma of the rectum. The latter lesion cleared on treatment with oxytetracycline and chloroquine.

Elsdon-Dew and associates have also had clinical experience with fumagillin. They have dealt with a more fulminating type of disease than was reported by any other workers using fumagillin. Elsdon-Dew's results were fairly poor with this therapeutic agent and he feels that it is not a satisfactory drug for use in amebiasis.

Amebic Hepatitis and Liver Abscess

In the past, emetine has been the drug of choice in the treatment of amebic involvement of the liver. Its effectiveness is well recognized, but many workers have been reluctant to use it because of its toxic effects, especially on the cardiovascular system. In the treatment of liver involvement emetine hydrochloride has been given in 65 mg. doses subcutaneously daily for 10 to 12 days. It is well recognized that at this dosage level from 50 to 100 per cent of the cases will show some toxic effects on the cardiovascular system. Most of the effects are discovered on serial electrocardiograms but some will show tachycardia, hypotension or other manifestations. A review of over 100 of our cases so treated re-

vealed evidence of cardiovascular toxicity in 73 per cent. Most of the manifestations were mild and promptly subsided on discontinuing the drug. In only one instance was it necessary to discontinue the emetine before the full course was given.

Since chloroquine has amebicidal properties and is concentrated in the liver, it has been used extensively in amebic involvement of the liver. The evidence to date suggests that in view of its effectiveness and the low incidence of toxicity, it is probably the drug of choice. The dosage schedule recommended is 0.9 gm. on the first day and 0.3 gm. daily thereafter for 20 days, giving a total of 6.9 gm. in 21 days.

The relative effectiveness of the antibiotics has not been finally established. The reported instances of the development of hepatic lesions, however, while the patient was receiving one of the antibiotics, casts considerable doubt on their effectiveness in the treatment of liver involvement.

Summary

In summary it may be said that today we do not have an amebicidal agent which is completely effective when used alone. The best results in the treatment of intestinal infections have been reported in the combination of oxytetracycline or chlortetracycline with other agents such as emetine, chloroquine, arsenicals and iodides.

Since emetine shows such a high incidence of toxic manifestations if given over long periods, its use should probably be restricted to cases with extra-intestinal lesions. Even then, the patient probably should not receive more than 65 mg. daily for 7 to 10 days.

Chloroquine is a relatively nontoxic substance in the dosage usually employed and is probably of the most value in treatment of extraintestinal lesions. Good results also have been reported in the treatment of amebic granulomas of the intestine with chloroquine and suggests its use in this condition in combination with oxytetracycline.

REFERENCES

1. Hargreaves, W. H.: Chronic Amebic Dysentery: A New Approach to Treatment, Lancet **2**:68-82, 1945.
2. McVay, L. V., Jr., Laird, R. L. and Sprunt, O. H.: Treatment of Amebiasis with Aureomycin, Southern M. J. **43**:308-313, 1950.
3. Armstrong, T. G., Wilmot, A. J. and Elsdon-Dew, R.: Aureomycin and Amebic Dysentery, Lancet **2**:10-12, 1950.
4. Most, H. and van Ansendelft, F.: Laboratory and Clinical Observations on Effect of Terramycin in the Treatment of Amebiasis, Am. J. Trop. Med., **31**:284-285, 1951.
5. Tobie, J. E., Most, H., Reardon, L. and Bozicevich, J.: Laboratory Results on the Efficacy of Terramycin, Aureomycin and Bacitracin in the Treatment of Asymptomatic Amebiasis, Am. J .Trop. Med. **31**:414-419, 1951.

6. Killough, J. H. and Magill, G. B.: Terramycin in Epidemic Typhus, Amebic Dysentery and Typhoid, J.A.M.A., **147**:1737-1740, (Dec. 29), 1951.
7. Martin, G. A., Garfinkel, B. T., Brooke, M. M., Weinstein, P. P. and Frye, W.W.: Comparative Efficacy of Amebicides and Antibiotics in Acute Amebic Dysentery, J.A.M.A. **151**:1055-1059 (March 28), 1953.
8. Killough, J. H., Magill, G. B. and Smith, R. C.: The Treatment of Amebiasis with Fumagillin, Science **115**:71, 1952.
9. McHardy, G., Bechtold, J. E., Welch, G. E. and Browne, D. C.: Fumagillin as an Amebicide, Southern M. J., **46**:428, 1953.
10. Black, R. L., Terry, L. L. and Spicknall, C. G.: Fumagillin in the Treatment of Amebiasis, Gastroenterology, **27**:87-92, (July), 1954.

Discussion

Dr. R. Elsdon-Dew (Durban, South Africa):—It is very nice to have you give me the opportunity to talk on amebiasis. I think my experiences are probably unequalled in that we have in one hospital alone some 2,500 to 3,000 cases per year of the acute ulcerative amebiasis; therefore I can talk with a certain authority.

I have listened to the discussion this afternoon with a great deal of interest and there are so many points, that I could probably discuss them all afternoon. I will bring out the main highlights that I have noted.

Dr. Rees referred to the taxonomic chaos which was a feature of the early days of our knowledge of the disease, and I would say that the taxonomic chaos is being replaced by another form of chaos. First of all, do we really understand what this parasite does? Is it in fact a definite pathogen, or is it only pathogenic when some other factor determines its pathogenicity?

Dr. Wright referred to the fact that in our area the disease is practically confined to one section of our community. Our community consists of three different races, the whites, the Indians, and the Africans, and those three communities are to all intents and purposes intimately mixed, and the incidence of the parasite in a healthy population is approximately parallel in all three cases; nevertheless, only in the African population do we see a great deal of ulcerative amebiasis, to them a very serious disease, a disease in which some eight or ten years ago there was a death rate of about 12 per cent of cases. When we see ulcers, they are from one end of the colon to the other, and there is not any question of whether there is involvement of the sigmoid only. That they are due to the amebae there is no doubt. If you look at the stool, there are literally myriads of amebae; so much so, we say we don't bother to move the slide. The amebae would walk off the cover. On occasion I have counted as many as 600 in a single field.

I should like to refer to other points which were brought up. Dr. Tobie referred to the difficulty of the identification of the parasite. I couldn't agree with him more. I don't think there is any organism causing disease more often misdiagnosed than is *Endameba histolytica*, and not only is the disease mis-

diagnosed, but, equally frequently, so is the association of the parasite with the disease which it is alleged to cause.

The incidence of *Endameba histolytica* in Great Britain is alleged to be on the order of 10 per cent, pretty much the same order as we have, and yet in Great Britain the disease is unknown.

In our part of the world we have a white population in which, though the incidence of the parasite is 10 per cent, there is practically no active disease. There are the usual vague symptomatologies which are so often attributed to the amebae. We have a local disease known as Natal fever, which is purely the laziness which one gets in a tropical climate, and which is very frequently attributed to the *Endameba histolytica*. I think I have heard of everything being attributed to the *Endameba histolytica*. The only thing I think I must draw the line on there, is pregnancy, but, after all, some pregnant people do have the *Endameba histolytica*.

The next point I should like to take up is Mr. Bozicevich's, on the complement fixation reaction. We do complement fixation reactions, and in our acute ulcerative cases, in which there is no doubt of the diagnosis, in which there are millions of amebae, as I have told you, we get only 56 per cent positive results. In liver abscess cases, with our antigens we have been getting up to 100 per cent. In a matter of, I believe, 200 cases, we have had but one failure of the complement fixation test of liver abscess. It is not unlikely that the 56 per cent positive which we get in the acute ulcerative form are due to amebae which have gone far beyond the bowel and are now perhaps in the liver, or elsewhere, and that brings me to the next point, which was brought up by Dr. Terry.

That is the question of the treatment. With this terrific amount of disease, we have been able to lay down a certain definite criteria for the selection of cases for trial therapy. Naturally, when we were confronted with this horrible number of cases, we had to devise some method of assessing the value, one way or another, of one or another method of treatment. We laid down certain criteria which we adhere to strictly, and up to date we have tested some sixty drugs.

Emetine and diodoquin were the first two we tried. We assessed them on sigmoidoscopy. The cases we use all have visible ulcers, and we have eliminated from such tests any cases with complications, because of the danger of losing them. Frankly, our results on emetine were not as good as Dr. Terry suggested. Our best results undoubtedly have been with wide-spectrum antibiotics, particularly terramycin and aureomycin, and more recently with the pure tetracyclines.

I noted that Dr. Terry got very good results with fumagillin. I am afraid I can't confirm it. Our results were so bad, frankly, that we stopped the series. We thereafter pushed up the dose to 200 mg. which is near toxic range, and

even then we got only a 40 per cent success rate, so I am afraid our results with fumagillin are not nearly as good as Dr. Terry's.

The next point is about the use of chloroquine. Chloroquine and emetine are both very effective drugs in extraintestinal amebiasis. Our success rate in the intestinal form is only some 50 per cent. Our success rate with chloroquine under the same circumstances was less than 10 per cent, but when it comes to the treatment of liver abscesses, either of these two drugs is so good that I don't think we need to go any further. Emetine and chloroquine are obviously effective because they are concentrated in the liver where they are most likely to get at the amebae.

I think that covers the main points except that I want to clear up one little thing which has been attributed to me, which is not quite true. Well, I will not say "not quite true", but, as I pointed out, three different races in our population get the disease in three different forms. When the African, who gets the disease most seriously, lives under rural conditions, he does not get the acute ulcerative form of amebiasis. It is only when he comes to town as a laborer, as a rule, that he imitates the whites and goes onto a diet of white bread, supplemented by jam, and gets very little protein. Instead of the milk he would normally drink in the bush, he takes to our little equivalent of Coca-Cola and Seven-Up, and that constitutes very largely his main diet.

I think that at this point I must give you briefly what my concept of the disease is. I do not think that *Endameba histolytica* is always pathogenic. I do think under certain circumstances, probably associated with a change in the bowel flora, following perhaps on a change of diet, particularly a diet of what one might call the lower carbohydrates, the amebae receive a stimulus to invade. Exactly what the nature of that stimulus is, we do not know. Thereafter the amebae invade and give us the disease. Without that stimulus, the amebae are unimportant.

Dr. J. P. Campbell (Wheaton, Ill.):—Does the intestinal form of amebiasis cause liver abscess without any invasion of the liver?

Dr. Elsdon-Dew:—That I don't really know, but I have for a long time suspected that it does, that you do get an enlargement of the liver without actual parasites. I think that accounts for a large number of the cases of so-called amebic hepatitis in which there is no abscess and no amebae in the liver. We have looked for amebae in the liver in those cases and have not been able to find them so far.

Dr. Emil Granet (New York, N. Y.):—This question pertains to amebic granulomas (amebomas), their frequency and their locations in the colon and rectum, their gross appearance as seen on sigmoidoscopy and finally, what is found microscopically after biopsy.

Dr. Terry:—I can't tell you why these lesions are more frequently located in the cecum and sigmoid areas. It may have something to do with the stasis of the intestinal contents in those areas. Certainly I think anyone else's guess would be as good as mine with regard to the cause.

Dr. Granet:—May I interrupt? I was interested in the specific percentages.

Dr. Terry:—I showed the slide which I believe indicated almost half located in the sigmoid-rectal area, about a quarter in the cecal area, 10 per cent in the transverse colon, and the others scattered about. With regard to describing the lesion, it may have almost any appearance. It may protrude from the wall of the bowel, have a somewhat spongy appearance, frequently be covered with necrotic material, which I think is probably the result of secondary bacterial invasion, and may commonly bleed easily on trauma, as on being touched with a curette or the end of the sigmoidoscope.

Any polypoid or redundant form can be assumed. In some instances they have been described as assuming a circular or annular form on the wall of the colon, without being particularly polypoid. So, I would say that there is an extreme variety in the form and appearance of these lesions.

Dr. Roy L. Sexton (Washington, D. C.):—Is there any prophylactic medication that might be taken over a period of time, or on a trip, to prevent infection with amebae? If it was mentioned, I might have missed it. I have in mind a Mr. D. of the Near East Department of an airlines who became rather tired of sending American families home with amebae, and tried two milibis tablets a day for two months. He is a resident manager and has not reported. It was thought to be worthwhile.

Dr. McCullough:—I will try to answer that. I think there has been no proven prophylactic treatment, although some of these intestinal drugs have been used for prophylaxis.

Our feeling is that if they are used in the absence of real proof of their efficacy, they should be used only for short periods of time, when a person is out in a highly endemic area. They should not be relied upon to take the place of other sanitary precautions, but the real answer as to how effective the prophylactic treatment of any of those drugs or carbarsones are, we do not know.

Dr. Victor Willner (New York, N. Y.):—What is the indication for liver aspiration in an amebic abscess, or surgical intervention in the treatment of amebic abscess?

Dr. Terry:—As to an indication for surgery, open surgery or drainage of an amebic abscess, to my mind, is never indicated. It is just about as close to never as any physician can come to making a rule.

With regard to aspiration, I am not certain. We have treated cases without aspiration and gotten satisfactory response over a period of time. Still, we have

felt that after the institution of therapy, the aspiration of these lesions probably hastened their regression. Whether this is true or not, I am not certain, and I would certainly like very much to hear from Dr. Elsdon-Dew on this question.

Question:—What is the indication for liver aspiration in an amebic abscess, or surgical intervention in the treatment of amebic asbcess?

Dr. Elsdon-Dew:—Actual open surgical intervention is never worthwhile, and it is outrageous if we can take the pus out otherwise, say by aspiration. Under those circumstances our liver patients do remarkably well.

Dr. Terry:—It is often surprising to realize how difficult it may be to hit large abscesses with the aspirating needle. Even though the lesion may be several cm. in diameter and may be well shown on x-ray films, one commonly encounters considerable difficulty in attempts at aspiration. It requires persistence and careful technic.

Dr. W. Stuart Henderson (Akron, Ohio):—Dr. Tobie's most interesting paper has largely answered the questions regarding laboratory diagnosis of amebiasis. A further combined question I would like to ask, is there any preliminary preparation for a patient presenting himself to the laboratory for a stool examination and what is the approximate length of time that the laboratory technician should spend examining a direct smear?

Dr. Tobie:—These are rather difficult questions.

First, I would prefer that the patient came in without preliminary preparation for stool examination. I think that under ordinary conditions that in this way a better specimen can be obtained for stool examination.

In regard to the length of time as to the technic of examination, a lot depends on the technician himself, how much experience he has, but certainly on a direct smear I would say not less than 20 minutes, and preferably longer.

Dr. McCullough:—I should like to add to that. I think that the time that the laboratory is asked to spend in establishing a diagnosis and finding of amebae should depend to some extent on how strongly the physician suspects the disease, and, if your suspicion is high, keep after the laboratory with specimens.

THE TREATMENT OF CELIAC DISEASE WITH THE SPECIFIC CARBOHYDRATE DIET

Report on 191 Additional Cases

SIDNEY V. HAAS, M.D.

and

MERRILL P. HAAS, M.D.

New York, N. Y.

Introduction

In 1950, we reported on 603 cases of celiac disease treated by us in private practice. During the three-year period following that report, we observed 213 additional cases long enough and closely enough to draw further conclusions concerning the diagnosis, prognosis, treatment, and clinical course under therapy of this disease. Of these, 22 were still open and under active treatment when the data for this paper were compiled. The remaining 191 have been followed-up after discharge with sufficient care and over a sufficiently lengthy period of time to warrant evaluation of total progress and outcome. Neither the data nor the conclusions reported here will deal with 64 cases which were seen by us only a few times in consultation or 127 cases which remained under our direct treatment and observation so briefly that their consideration in a scientific report is unjustified.

Diagnosis

Our studies of these 191 cases fortify the point that we have stressed elsewhere—that the diagnosis of celiac disease depends primarily upon a history of prolonged intermittent soft-loose, frequent, foul, and mucus-laden stools occurring in a child between the ages of six months and three years and occasionally in younger or older children. The tentative diagnosis is confirmed by the administration and subsequent withdrawal of the specific carbohydrate diet. That is, the patient is placed on the diet until his symptoms abate. He is then restored to his ordinary diet. If the original symptoms then recur, diagnosis of celiac disease is confirmed and the patient again placed on the therapeutic diet for the full course of treatment. We know of no laboratory procedure for the diagnosis of celiac disease. Complex and time-consuming tests for fecal fat and starch, gastrointestinal x-ray series, hematological studies, plotting of blood-sugar and Vitamin A tolerance curves, and analyses of duodenal enzymes may be useful when it becomes necessary to rule out conditions simulating celiac disease such as tuberculosis, intestinal parasites and fibrocystic disease of the pancreas.

One point of diagnosis that must be stressed is the age at which symptoms first occur. As our figures (Table I) show, the first symptoms usually manifest themselves between the ages of nine and ten months. There is, however, a sig-

nificant number of cases in which the onset of symptoms takes place anywhere between birth and the ages of three and four years, so it is inadvisable to rule out a diagnosis of celiac disease on the basis of any age factor by itself. It is interesting to note (Table II) that the vast majority of cases did not come to our attention until the symptoms had persisted for periods ranging from three months to more than two years. In 31 cases, the symptoms had persisted for considerably longer than two years before the patients were placed on the specific carbohydrate diet.

One child had suffered from celiac disease for more than eleven years before he came to our attention. It is interesting to note, further, that more than half the patients reported in this paper had been under the observation of one or more physicians for celiac disease before they were presented to us.

TABLE I

AGE AT ONSET

Birth	35
2 days-6 months	29
6 mos. plus-1 year	50
1 yr. plus-2 years	64
2 yrs. plus-4 years	8
Over 4 years	5
Total	191

While our data (Table III) shows that many of these patients had been diagnosed as suffering from celiac disease and had been treated on that basis, many others had been treated for allergy, simple diarrhea, and unspecified ailments. It is interesting to note further that, in most cases, careful questioning elicited the fact that there had been episodes of loose stools for brief periods before the onset of the more persistent diarrhea. A second point we wish to make about diagnosis concerns the state of nutrition of these children at initial presentation. As our figures (Table IV) show, the weights at first examination were not significantly below the means for the age groups. Only 24 per cent of the cases were more than one standard deviation below the mean. In other words, the great majority of cases of celiac disease seen by us in the New York area did not show any great degree of retardation in weight. As a matter of fact, 62 per cent of the cases were well within the normal weight range while 13.5 per cent exceeded the norm. This indicates that a diagnosis of celiac disease cannot be ruled out of consideration simply because a child is either within or above the normal weight range for his age. Even though we have observed that the weight at initial presentation is not particularly significant in diagnosing celiac disease unless the loss is excessive, nevertheless we feel that the general state of nutrition as observed clinically and as determined by the estimates of parents is an important diagnostic guide. The state of a child's nutrition must be judged

by estimating and evaluating such imponderable and intangible factors as tissue and muscle tone, hair and skin quality, brightness of the eyes, general strength and vigor, etc. Upon initial presentation, all of our cases, even those whose weights exceeded the norm by one standard deviation or more, showed clear signs of poor nutrition when evaluated on the basis of the factors mentioned above.

Specific Carbohydrate Diet

All of the cases reported in this paper were treated by means of the specific carbohydrate diet which we have described in earlier publications. Reference to our data (Table V) shows that we were able to place 190 of the 191 patients reported in this paper on carbohydrates, other than those permitted in the therapeutic diet within 18 months after the start of treatment. Among these formerly forbidden carbohydrates were the starches and complex sugars contained in such foods as bread, potatoes, cookies and candies. One hundred

TABLE II

Onset to Initiation of Specific Carbohydrate Diet

Under 3 months	28
3 mos. plus-6 mos.	33
6 mos. plus-1 year	38
1 yr.-2 yrs.	61
2 yrs.-3 yrs.	10
3 yrs.-4 yrs.	10
4 yrs.-5 yrs.	3
5 yrs.-6 yrs.	3
6 yrs.-7 yrs.	4
11yrs. and 8 mos.	1

seventy-five of these patients were permitted starches and sugars within 15 months after they had commenced the specific carbohydrate diet. The introduction of these carbohydrates to the diet is the point at which it is safe to assume that the patient is on the road to comparatively rapid recovery. Thereafter, we are able to introduce previously untolerated foods in such rapid succession that our patients are allowed a completely unrestricted diet from 18 to 24 months after treatment has been started. Further reference to the figures (Table V) show that more than 81 per cent of our cases could take whole milk within 18 months after treatment had started and an additional 12 per cent could take whole milk within 24 months after they had been placed on the specific carbohydrate diet. The one case that took more than 18 months before he could take starch and sugar and more than 24 months before he could tolerate milk was a patient whose attendance at our office was extremely irregular and whose parents found it difficult to cooperate in managing the diet.

Although the details of the specific carbohydrate diet have been given in earlier reports, we feel that it is wise to discuss a few of the important features. One basic principle of the diet must be established firmly and reiterated persistently: *No food may be ingested by the celiac patient that contains an appreciable amount of carbohydrate other than that found in fruits and to a lesser extent in vegetables, and in protein milk.* The basis of the specific carbohydrate diet is ripe banana and protein or calcium caseinate* milk. As emphasized earlier, the foods prescribed in this diet have been selected because clinical experience has shown them to be effective in the treatment of celiac disease. From this empirical evidence, we have drawn the conclusion that the common denominator of all the foods permitted in the specific carbohydrate diet lies in the preponderance of monosaccharides in the carbohydrate portion. We believe that sufferers from celiac disease are intolerant to all but monosaccharides. It is our theory that polysaccharides act as the exciting cause of the diarrhea. The term, polysaccharides is used in its literal sense—any carbohydrate whose molecule contains more than six carbon atoms. This includes disaccharides such as sucrose, lactose, and maltose as well as dextrins and starches.

Although all fruits may be used later, banana is the most satisfactory and the only safe fruit to be used at the outset of treatment. Because various other fruits have qualities which tend to make them laxative, they must be employed judiciously when diarrhea is still active. There need be no curtailment of the amount of banana given. Most canned fruits are forbidden because of the added sugar they contain. If cooked fruits are desired, they may be prepared with synthetic sweeteners by the family, but the initial product must be known.

In addition to protein milk and fruits, the specific carbohydrate diet may contain proteins in any form and fats in moderate quantities. Thus meat, fish, and fowl of any kind may be used, and it is not necessary or even desirable to have the fat removed. All cheese is satisfactory, unless it has been processed by the addition of ingredients to alter its composition. The diet may include any cheese in its initial form: Swiss, cheddar, American, münster, edam, and of course pot cheese.

Gelatine is given for dessert in this diet, but none of the prepared gelatine desserts which contain sugar. Desserts made from pure gelatine, fruit juice, and synthetic sweeteners are well tolerated. Honey, dates, and raisins may be

*Casec Milk:—

Casec	4 tablespoons
Water	1 pint
Whole Milk (not homogenized)	1 pint

Mix the Casec with a little cold water (enough to form a smooth paste), pour in the remainder of the cold water, then pour in the milk, and bring the whole mixture while stirring constantly to a boil, then boil actively for one minute. Remove from fire. Let cool. If necessary to sweeten, use one or two tablets of saccharin. (One grain).

used for confections, but some dates are packed in sugar syrup and these should be avoided.

When brisk diarrhea is controlled, egg is added to the diet, and when the stools are formed and occur no more than two or three times daily, vegetables are given. The latter, however, must be added to the diet cautiously, one at a time, with a sufficient period between each new introduction to determine their effect. In some cases diarrhea recurs when vegetables are ingested, in which case their use must be postponed. In general, lettuce, tomato, string beans, squash, and carrots are well tolerated. Canned vegetables are not to be used unless sugar-free. Potatoes may not be used.

Fats in association with meats in the normal amounts, in the form of butter, and that existing in protein milk are well borne. Sour cream is usually tolerated. The only restriction on fats may come at the beginning of the diet, but when a full and well-rounded diet has been established, there need be no restrictions of fat beyond that usually exercised in the diet of healthy children.

With the inclusion of the foods mentioned, the specific carbohydrate diet is complete. Since it is full and well-balanced, it is continued for at least one year, supplemented by certain vitamins. Vitamins A and D should be administered, but cod liver oil is usually not well tolerated. Some of the newer preparations of aqueous soluble A and D are excellent substitutes. One of the preparations of B-complex, including folic acid, seems to be desirable. Since anemia is a regular concomitant of celiac disease, iron in some form is called for.

In prescribing this diet, it is almost more important to stress what is *not* fed than what is fed. Any cereal grain is strictly and absolutely forbidden, including corn, wheat, rye, or rice in any form, whether as bread, cake, toast, zwieback, crackers, cookies, or breakfast cereals. Potatoe is prohibited. Sugar is forbidden as sweetening or in the form of candy, pastries, breads, etc., as well as dextrins such as are found in corn syrups and lollipops. Whole milk, per se, is not allowed.

We realize, of course, that even in the specific carbohydrate diet, certain polysaccharides are present, such as the lactose in the protein milk and some sucrose in the fruits. It is quite possible, as a matter of fact, that a diet restricted to protein, fat, and carbohydrates solely in the form of glucose and levulose might achieve the desired results more quickly than they are achieved with the specific carbohydrate diet. We also realize, however, that we are dealing with children who derive pleasure and other emotional satisfactions as well as nutrition from their foods, and not with automatons or laboratory animals. Therefore, in treating sufferers from celiac disease, it has been felt necessary to strike a compromise between a normally palatable and acceptable diet and one in which the restriction of polysaccharides was total. The resulting specific carbohydrate diet represents this compromise. The fact must also be stressed that a diet cannot be constructed solely on the basis of ailments that must be

restricted—it must also be based on food elements which must be included if the diet is to provide optimum nutritive value. We have seen many cases where children have been placed on diets that succeed in eliminating all or most polysaccharides but which fail to provide for such necessary elements as adequate fat and protein intake, and which completely neglect such important factors as palatability, variety, and appetite appeal. The state of nutrition of such children upon initial presentation to us was such as to make it quite clear that either the diet had not been followed, or, if followed, had not provided for even minimum nutrition.

Dietary supplements such as vitamin concentrates, especially Vitamins A and D, are valuable and advised. The use of such other supplementary medicaments, opium, kaolin, pectin, etc., is of little value. In many of our cases, we have observed the immediate effects of the sulfonamides, penicillin, and occasionally the mycins in causing a temporary cessation of the diarrhea. We have occasionally employed penicillin in the early stages of treatment, especially when the patient has been suffering from an upper respiratory infection or when so-called "virus intestinal grippe" was prevalent. Although the effects of these medications are immediate, however, they are merely transitory and do not,

TABLE III

TREATED FOR CELIAC DISEASE BY METHODS OTHER THAN SPECIFIC CARBOHYDRATE DIET

Yes	66
No	27
Not Stated	98
Total	191

in themselves, result in a permanent cessation of symptoms. We have seen many cases where such antibiotic therapy prescribed by other physicians has resulted in apparent cures only to be followed by recurrences after the medications have been withdrawn. For this reason, we feel that the antibiotics are of true value only in treating infections associated with celiac disease and not in treating the disease itself.

There is one group of drugs which has been found to be useful and which we recommend. These are the anticholinergic drugs. We have been accustomed to prescribe atropine sulfate, although some of the newer synthetic anticholinergic agents seem to be promising. We employ atropine in ascending small increment dosages to levels where symptoms are ameliorated or eliminated. Symptoms of enterospasm such as colicky pain or vomiting indicate the use of such drugs.

SO-CALLED "GLUTEN FACTOR"

During the past few years, many investigations on the role of a so-called "gluten factor" in the cause and dietary treatment of celiac disease have been

reported in the Dutch and British literature. The burden of the conclusions drawn from these investigations is that there is some substance in the gluten fraction of wheat flour which produces the symptoms of celiac disease, and that, therefore, a diet completely free from this substance will result in the elimination of the symptoms. In clinical practice, this is achieved by removing all forms of wheat from the celiac patient's diet.

A recent contribution contains the following conclusions, which begin to substantiate our thesis that the offending substance or substances are in the carbohydrates. It would be a great contribution if it were possible to isolate the factor which clinically has been recognized for such a long time.

"1. A factor exists in wheat which is the cause of anorexia, vomiting, diarrhea and a large proportion of the fat elimination in patients with celiac disease. However this factor is not in the starch.

"2. Although anorexia, vomiting, diarrhea and steatorrhea are produced or exacerbated by the 'wheat factor' there is no quantitative relation between these symptoms.

"3. The 'wheat factor' has so far been encountered in wheat, rye and oats.

"4. It is possible and perhaps even probable that this factor will also be found in other foodstuffs which have not yet been tested.

"5. It is probable that the 'wheat factor' is active in other disturbances as well as celiac disease (indigenous sprue, some forms of subacute dyspepsia, and enteritis in infants and small children.

"6. The effect of the 'wheat factor' may be of importance for the recognition and understanding of nutritional and intestinal disturbances.

"7. In investigation of improvements produced by medication or vitamins in cases of celiac disease, the experimental setup must take into account the 'wheat factor' in order to avoid wrong conclusions."

An examination of Table I will show that more than 18 per cent of the cases reported in this paper had their first symptoms of celiac disease at birth, and an additional 15 per cent manifested their first symptoms between the ages of two days and six months. In other words, in a significant number of cases, the onset of the symptoms of celiac disease took place prior to the period of the feeding of solid foods. This fact, it seems to us, must cast some doubt upon the validity of the gluten-factor hypothesis. Another interesting fact leads us to question this theory. For a variety of reasons, including the frequent misconception of celiac disease as starch intolerance, it is common practice in New York City as well as in other parts of the United States to attempt a cure by prescribing a completely wheat-free and starch-free diet. Our experience has demonstrated that such diets, *unless they also eliminate other polysaccharides aside from those in wheat and starch,* do not succeed in removing the symptoms. Furthermore,

upon recovery by means of the carbohydrate free diet at once, wheat is used in liberal quantity without ill-effect.

In considering the work of the British and Dutch investigators, another fact about celiac disease must be taken into account. This illness has many of the aspects of a stress syndrome that make its clinical course in relation to any single change in environment or other conditions over a short period of time erratic and difficult to evaluate. For example, even the most severe case of celiac disease will show improvement in appetite, weight, and condition of stools if placed in a hospital bed under conditions of minimum exertion, regardless of the diet administered. Conversely, the literature abounds with reports of cases who were doing well under proper dietary regimens and who showed recurrence of all symptoms as a result of such apparently minor stresses as mild upper respiratory infections, the eruption of teeth, or increased emotional tension in the home. Therefore, in evaluating the effects of any given dietary change on hospitalized cases of celiac disease such as are reported in the British and Dutch literature, such factors as ward routine, bed rest, change from home environment, intermittent mild infections, etc., must be considered.

TABLE IV

WEIGHT DEVIATIONS AT START OF SPECIFIC CARBOHYDRATE DIET AND INCREMENT DEVIATIONS AFTER ONE YEAR OF TREATMENT

	Minus one or more Standard deviation	Plus or minus one Standard deviation	Plus 2 or more Standard deviation
At start	46	119	26
After one year	17	160	24

We feel, further, that day to day fat balance studies over comparatively short periods of time, such as are reported in the literature, do not contribute significantly to the evaluation of any given dietary regimen, because the course and treatment of celiac disease must be judged in terms of total effect on the patient over an extended period. It is not enough to place a diarrhea-wracked and severely undernourished and underweight child on a prescribed diet and to pronounce that diet successful and the patient cured simply because the diarrhea has stopped, there has been a gain in weight, and the laboratory tests have shown an improvement in fat balance. *We maintain that the criterion of successful treatment of celiac disease must be perfect nutrition and health with complete cessation of diarrhea within a period of 12 to 18 months after the initiation of therapy regardless of what foods are included in the diet thereafter.*

MANAGEMENT AND EVALUATION OF PROGRESS

Once a definite diagnosis has been made and the specific carbohydrate diet has been prescribed, the problem of management in celiac disease has just begun. This is true because the illness is not a simple physiological derangement

which can be quickly corrected. The correction of the slowly and chronically developing symptomatology must be expected to be correspondingly slow and protracted. Under proper treatment by means of the specific carbohydrate diet, however, improvement should be steady and progressive until all symptoms have been corrected and there is no recurrence of such symptoms even when the patient is taking a full normal diet. Specifically, this means that the chief symptom, diarrhea, cannot be expected to disappear within a few days after the initiation of treatment, although such rapid improvement may occur in

TABLE V

TIME ELAPSED BETWEEN START OF SPECIFIC CARBOHYDRATE DIET AND INTRODUCTION OF STARCH AND MILK

	Starch and Sugar	Milk
Under 8 months	1	
8 months	1	
9 months	1	
10 months	2	
11 months	28	
12 months	85	6
13 months	30	12
14 months	15	27
15 months	12	44
16 months	2	35
17 months	3	20
18 months	10	13
19 months		5
20 months		8
21 months	1	4
22 months		4
23 months		3
24 months		8
More than 24 months		2
Totals	191	191

some cases. Our data (Table VI) show that in 38 per cent of the cases reported in this paper, the diarrhea was under control within one month after the inception of treatment. Of course, this rapid correction of the chief and most distressing symptom of celiac disease is desirable not only because it indicates satisfactory progress, but because of its beneficient psychological effect upon the patient and his family. The persistence of the diarrhea for longer periods ranging, in some cases, up to ten months, however, does not mean either that progress toward curing the disease is unsatisfactory or that the nutritional state

of the patient is not improving. Conversely, the control of the diarrhea does not, by itself, indicate satisfactory progress. We have seen numerous cases where diarrhea has been checked by such means as the administration of antibiotics, rigorous limitation of food intake, etc., without any concomitant improvement in the patient's nutritional condition.

Occasionally, there is a recurrence of loose stools after the initial severe diarrhea has been brought under control. When this occurs, an explanation must be sought in two possibilities: a lapse in the specific carbohydrate diet or an infection such as an overt upper respiratory infection, a so-called "intestinal grippe" in which upper respiratory involvement may be minimal, etc. In the first case, reinstitution of the strict diet will again bring the diarrhea under control. In the second case, the condition will be corrected when the infection subsides.

We have observed that the most outstanding and, frequently, the earliest and most dramatic signs of improvement in the child suffering from celiac

TABLE VI

CONSTITUENTS OF DIETS TO INTRODUCTION OF SPECIFIC CARBOHYDRATE DIET

Wheat*	109
Potatoe	52
Sugar†	94
Milk‡	123
Banana	57

*includes bread, cereal, spaghetti, pastina, etc.
†includes candy, jello, sugared fruits, etc.
‡includes hypro, Mul Soy, plain and skimmed milk, goat's milk, buttermilk, etc.

disease takes place in the area of behavior. All students of celiac disease have emphasized the fact that a cardinal symptom of the illness is irritability expressed in every manner of capricious and almost uncontrollable behavior. Within a week or two after the initiation of therapy, the patient is less irritable, more cooperative, more pleasant, and happier. In many instances, parents have reported dramatic improvement in behavior within a few days after the beginning of the specific carbohydrate diet. In other cases, especially where the patient is an only child and there is little basis for comparison, the parents have not initially reported any behavior symptoms. Within a few weeks, however, they remark that the present happy and pleasant condition of their child now convinces them that there had been behavior difficulties prior to the institution of treatment. In this connection, a return to irritable behavior after the condition has been rectified has occasionally been the clue to the discovery of some lapse in the diet or to some hidden infection. When these conditions have been corrected, behavior again improves.

Most important in evaluating the progress of treatment, is the observation of the nutritional progress of the patient at frequent intervals. This is done in three ways. First, is the obvious method of charting growth as indicated by height and weight figures. As we have pointed out, however, this method by itself may be misleading, since a patient may exceed the norms and still be in relatively poor nutritional condition. Second, is the parent's appraisal of improvement in strength, endurance, fatiguability, appearance, behavior, and general physical condition. Third, and most important, is the clinical judgment and appraisal of certain intangible and imponderable factors and impressions which converge to convey to the experienced and perceptive physician a total picture of the child. If progress is satisfactory, the skin should be soft, smooth, silky, elastic, and of good color. The carriage should be erect, and the muscles, especially in the abdominal and facial regions, firm, well-developed, and of adequate power. A striking example of this is the reduction in size of the distended abdomen after good muscle tone has been maintained for a sufficient length of time. Although it is difficult to describe the factors and impressions that contribute to the clinical judgment, all practicing physicians are familiar with them. The important criterion in evaluating progress in this respect is not so much the rate of improvement as it is the steadiness and continuing nature of the improvement.

"Celiac Crisis"

Many investigators refer to the so-called "celiac crisis". Most recently, di Sant Agnese reported that crises occurred in more than 60 per cent of a series of patients studied at Babies Hospital. Such episodes are said to take place in severe cases, especially among younger children during the early stages of treatment. According to the reports, such crises occur when a parenteral infection or some other cause precipitates an intense watery diarrhea. Within a few days, this results in such severe dehydration and electrolytic imbalance that hospitalization and intravenous feeding become necessary. Although such incidents prior to consultation with us have been reported by parents, we have never experienced such a crisis with severe dehydration or with electrolytic imbalance in any patient who has been treated with the specific carbohydrate diet. We have not seen such crises even though, in some of our cases, a parenteral infection has precipitated a diarrhea of as many as eight to ten watery stools a day for a few successive days. The only possible explanation we can offer for the discrepancy between our experience and the experience of some other investigators is that the specific carbohydrate diet reduces the intestinal irritation to a point where the superimposed irritation caused by the parenteral infection no longer produces excessive stress.

Stress and the Autonomic Nervous System

Though peripheral to the main problem, two aspects of celiac disease have engaged our attention. These are the factors of stress and of the role of the

autonomic nervous system. Although the degree of stress and autonomic nervous system involvement may vary from case to case, they are present in all patients suffering from celiac disease.

We have been particularly interested in observing the relationship of stress to the outstanding symptom of the illness, diarrhea. Regardless of the type of dietary management, certain stress situations seem to be consistently associated with increased diarrhea. Among such stress factors are infections ranging from severe involvements of the upper respiratory tract to furunculosis, prolonged pain such as is associated with teething, unusual or excessive physical exertion, and irritating emotional situations at home or elsewhere. One mother, for example, called our attention to the fact that her child had a soft, foul stool on the day of each visit to the doctor's office. Apparently, the combination of travel, disarrangement of normal daily routine, introduction to an unusual environment, and the examination procedure itself set up a stress situation which precipitated the diarrhea. We have observed, conversely, that the removal of a stress situation

TABLE VII

TIME ELAPSED FROM INITIATION OF SPECIFIC CARBOHYDRATE DIET TO CONTROL OF DIARRHEA

Within one month	73
1-2 months	17
2-5 months	58
6-10 months	24
11-14 months	5
Formed at start	14
Total	191

may result in a cessation of the diarrhea. Such changes as removal to a hospital with its attendant bed rest and ward routine, the subsidence of teething, or the complete acceptance and integration of a new sibling in the home frequently result in the elimination of diarrhea. These clinical observations seem to be in accord with the findings of Adlersberg and his co-workers on the effects of cortisone in relieving the symptoms of sprue in adults. In this connection, it is also interesting to observe that, just as the withdrawal of cortisone resulted in the recurrence of the sprue symptoms, so does the restoration of the stress situation cause a renewal of the diarrhea. It is important to note, however, that the longer the child has been on the specific carbohydrate diet, the less likely he is to react to stress situations with episodes of diarrhea. Whether this beneficial effect is accomplished because the specific carbohydrate diet withholds additional intestinal irritants in the form of polysaccharides or because the diet promotes a nutritional state in which the body is able to combat the stress forces more effectively, remains to be determined.

Certain facts have led us to conclude that there is an important relationship between celiac disease and the autonomic nervous system. As can be observed in Table VIII, a large number of our cases show family histories of hypercholinergic activity manifested in such complaints as nervous stomach, diarrhea under tension, duodenal ulcers, etc., in parents, grandparents, and siblings. Many of our celiac patients, themselves, reveal an early history of hypercholinergia as shown by spitting, vomiting, or colic during the neonatal period. Furthermore, in many active cases of celiac disease, there are direct signs of a hypercholinergic state. Some of these are vomiting, abdominal cramps, excessive secretion of the mucosa of the bowel, and skin capillary changes resulting in pallor or rapidly changing mottling of the skin. In view of the fact that cholinergic blocking agents, notably atropine, are extremely beneficial in relieving many of the symptoms listed above, especially vomiting and abdominal cramps, one is led to speculate on the possible relationships between celiac disease and stress, the autonomic nervous system, and adrenal function.

Psychological Considerations

The earliest and all succeeding literature on celiac disease stressed the behavior disturbance in these cases, calling attention to the unhappy faces, the extreme irritability, the desire to remain undisturbed and not be touched, hyperesthesia, anorexia, more rarely bulimia, and numerous other aberrations of conduct. Through the years, this phase of the disease has attracted the attention of observers and has been given a prominent place in the symptomatology.

As long ago as 1923, Hablutzel-Weber stressed the role of psychological factors in celiac disease. Since then, many investigators, notably Schiff, have also discussed this matter. In one of our earlier publications, we considered the psychosomatic aspects of celiac disease in some detail. A recent report by Prugh, which emphasizes the effect of the mother's personality on the child suffering from celiac disease, however, makes it desirable to review and reconsider the psychological aspects of this illness.

There is no doubt that there are psychological relationships in celiac disease as well as in most other diseases. Such factors as parental anxiety, personal and environmental tensions, sibling rivalries, etc., may have some influence in exacerbating the basic symptoms. Our clinical experience has shown that the alleviation of these psychotraumatic conditions may result in transitory amelioration of these symptoms. Celiac disease, however, involves a basic physiological disorder, which usually can be permanently corrected only by strict dietary control, and to treat this illness by psychological methods exclusively will, at best, be only temporarily successful.

Prugh's report is based on studies of 14 celiac patients and their mothers. His basic conclusion is that the mothers showed rigidity of personality, marked anxiety, and a tendency toward over-cleanliness. Prugh maintains, further, that

there is "a consistent though nonspecific type of emotional disturbance on the part of each of the children, antedating the onset of clinical symptomatology and arising as a result of the disturbed mother-child relationship." He implies, therefore, that this "disturbed mother-child relationship" is a primary cause of celiac disease. Since our data (Table I) show that a considerable percentage of cases manifested their first symptoms at birth or very soon thereafter, some doubt must be cast upon this implication. We feel, on the other hand, that the nature of this disease is such as to provoke just such personality defects as Prugh describes

TABLE VIII

FAMILY HISTORY

Celiac disease	31
Digestive disturbances	24
Allergies	31
Unknown	65
Nervous stomach	21
Diarrhea	12
Asthma	16
Cancer	16
Diabetes	28
Colic	2
Hypertension	11
Ulcer	11
Nervous or Spastic Colon	3
Colitis	2
Gallbladder disorder	2
Constipation	2
Hernia	1
Rheumatic fever, rheumatic heart	5
Headaches	2
Arthritis	2
Heart disease	2
Epilepsy	1

in the mothers of patients. Inasmuch as the outstanding symptom of the disease is a chronic and foul diarrhea, and inasmuch as uncertain and prolonged prognoses are frequently given and even satisfactory dietary treatment involves severe demands upon the mother's patience, endurance, and ingenuity, we would normally expect them to be disturbed.

We have been strongly impressed by the fact that the celiac patient exemplifies a somatopsychological rather than a psychosomatic relationship. That is, we feel that the physiological aspects of the illness are the primary cause of the

emotional and behavioral disturbances rather than the converse. The personality of the child who is suffering from celiac disease is largely determined by his nutritional state, and the latter is directly dependent on the diet which he receives. In the early stages of almost all our cases, there was some degree of irritability which was expressed in such ways as aggression, withdrawal, capricious behavior, temper tantrums, etc. Often the parents have complained of these personality problems and they have frequently been apparent to us at the first consultation. In such cases, there was a rapid improvement of personality within a few weeks after initiation of treatment by means of the specific carbohydrate diet. Parents usually reported that the temper tantrums stopped, the child became more cooperative and tractable, and there was a general improvement in personality and behavior within a short time after treatment had started. In a few outstanding cases, it was clear to us that the parents had become emotionally disturbed as a result of their children's disease. Some of them could not refrain from tears when they described the symptoms during the first consultation. In such cases, the improved nutritional and psychological state of the patients was soon reflected in a similar improvement in the psychological state of the parents. We do not intend to minimize the role of psychological factors in determining the course of celiac disease, nor have we overlooked the possibility that the tensions involved in handling a sick child may bring to the surface latent personality problems in the parents. We do, however, feel that the correction of the nutritional disorder is basic and primary to the improvement of the personality. There are a few families in which guidance and psychological support is necessary even after the patient has been cured of celiac disease, but this is common in the treatment of all diseases in the practice of pediatrics.

The typical psychological picture of the celiac sufferer is such a common and pronounced symptom that it should be considered in making a diagnosis. Furthermore, the relationship between improved nutrition and improved personality is so consistent that it can be used as a guide toward judging progress. When a child who has been doing well on the specific carbohydrate diet suddenly becomes irritable again, it is advisable to make careful inquiries as to whether or not the diet is being strictly maintained. This method can be of great help in enabling the physician to check on the degree of cooperation he is getting from the parents.

Parents frequently express the fear that rigid adherence to the specific carbohydrate diet may cause frustrations and personality problems in their children. They point out that the celiac sufferer may resent the fact that he is deprived of the bread, cake, and candy which his siblings and friends enjoy. Our experience has shown that the rigidity of the diet, when the child is sensibly handled by parent and physician alike, does not create behavioral and emotional difficulties. In the first place, the dietary restrictions, unlike those that must be imposed in some diseases, are temporary. In the second place, it has been possible to help mothers to provide a satisfying and varied diet which

includes carbohydrate-free cakes, candies, and other sweets despite the restrictions. Far from injuring the personalities of children suffering from celiac disease, we find that the specific carbohydrate diet helps them to become happier and better integrated. In connection with this, it is interesting to note the reaction of cured patients to candy even after they are permitted a full and unrestricted diet. Most of these children eat so little candy that their parents do not have the usual problem of confining the consumption of sweets to a reasonable limit.

To summarize, we have learned that the personality pattern of the child with celiac disease is directly dependent upon strict adherence to the diet. If the slightest amounts of starches or polysaccharides other than those permitted in the specific carbohydrate diet are either deliberately or inadvertently introduced, the child will be irritable, relatively unhappy, and poorly adjusted. When the diet is carefully supervised, the child will be happy, pleasant, and tractable. We have learned, furthermore, that there are neither temporary nor permanent adverse personality sequelae as a result of strict adherence to the specific carbohydrate diet.

Cure

Various definitions of cure in celiac disease have been promulgated, each depending on the objectives that the individual investigator hopes to achieve. Some pronounce a patient cured when he no longer suffers from intractable diarrhea leading to dehydration and death. Others are satisfied if a child has only occasional bouts of diarrhea. Yet others feel that the optimum goal has been achieved when diarrhea is controlled by diet even though the special diet must be continued indefinitely and though lapses result in recurrence of symptoms. We feel that none of these constitute true cure of celiac disease. Our objective is a child who shows excellent nutrition, an adequate and happy personality, complete absence of stool abnormality without even temporary diarrhea over short periods, and who can eat a completely unrestricted diet without any recurrence of symptoms. All of the above should be achieved and usually are achieved after a maximum period of 18 months of treatment. Only when all of these objectives have been attained do we consider a celiac patient to have been cured.

Some pediatricians claim that children "outgrow" celiac disease by the time they are six or seven years old without any treatment whatsoever. Even if this were true, and the fact that we have had a number of patients in their pre-teens tends to cast doubt upon this assumption, such a period of suffering while waiting is completely unnecessary. We feel that it is far better to prescribe a rigid diet for 12 to 18 months and thus to achieve a complete cure, rather than to impose a short-term rigid diet which must, of necessity, be reimposed periodically when the patient's symptoms recur while on a normal diet. In other words, if the specific carbohydrate diet is followed for a period of from 12 to 18 months with-

out any lapses whatsoever, then the physician can confidently predict that the patient will be able to return to a full and normal diet without any recurrence of symptoms and without any necessity for any return to dietary restrictions*

In the large majority of our cases, the nutritional state has become excellent between six and nine months after the start of treatment. It is, however, our practice to continue our patients on the specific carbohydrate diet for a minimum of 12 months. Then starches and sugars are added. If there are no adverse results, the diet is slowly extended until it is normal. If the addition of carbohydrates causes a return of the symptoms, the therapeutic diet is reinstituted for an additional three to six months. In only one of the cases reported in this paper were we forced to continue a patient on the diet beyond 18 months, and this was caused by lack of parental cooperation both in maintaining the diet and in bringing the child in for regular examination and evaluation. The other 190 patients tolerated starch and sugar without any recurrence of symptoms within 18 months after initiation of therapy. Examination of Table V will show that 175 of these children were given starch within 15 months after starting treatment, and 118 were on starch after 12 months of treatment with the specific carbohydrate diet.

BIBLIOGRAPHY

Adlersberg, D. et al: Studies on the effects of cortisone and pituitary adrenocorticotropic hormone (ACTH) in the sprue syndrome, Gastroenterology **19**:674, 1951.

Anderson, C. M. et al: Celiac disease: Gastrointestinal studies and the effect of dietary wheat flour, Lancet, **262**:836, 1952.

Dicke, W. K.: Celiac disease; investigation of the harmful effects of certain types of cereal on patients with celiac disease, Thesis, Utrecht, 1950.

Dicke, W. K. et al: Celiac disease: The presence in wheat of a factor having a deleterious effect in cases of celiac disease, Acta Paediat. **11**:224, 1953.

Di Sant'Agnese, P. A.: Idiopathic celiac disease: course and prognosis, Pediatrics **11**:224, 1953.

Haas, S. V. and Haas, M. P.: Diagnosis and treatment of celiac disease: report of 603 cases, Postgrad. Med. **7**:239, 1950.

Management of Celiac Disease, J. B. Lippincott, Phila., 1951.

Hablutzel-Weber: Concerning intestinal infantilism and the fate of its victims, Inaug. Diss. Zurich, 1923.

Prugh, D. G.: A preliminary report on the role of emotional factors in idiopathic celiac disease, Psychosom. Med. **13**:220, 1951.

Schiff, E.: Celiac Disease, Urban, Berlin and Vienna, 1934.

Sheldon, W.: Celiac disease, a relation between dietary starch and fat absorption, Arch. Dis. Childhood **24**:81, 1949.

Sheldon, W. and Lawson, D.: The management of celiac disease, Lancet, **263**:902, 1952.

van de Kamer, J. H. et al: An investigation into the injurious constituents of wheat in connection with their action on patients with celiac disease, Acta Paediat. **42**:223, 1953.

*In sprue, which is an adult celiac disease, the condition is irreversible and although cure results from a carbohydrate specific diet, relapses will occur through the years requiring several weeks or months of dieting to overcome it.

Report of the Research Committee of the American College of Gastroenterology

Gastrointestinal diseases are among the most frequent ailments. Yet, gastroenterology has not taken the place in medicine, education and research that it deserves. There are few laboratories, engaged in basic or in clinical research of gastroenterology, and few medical schools offer special courses in gastrointestinal disease. Also, opportuntities for training in gastroenterology, both in the basic and in the clinical branch, are sadly deficient.

The cause of this may be, that most gastrointestinal diseases are not killers, as for instance coronary disease. This seems to have led to less publicity and less interest in the field by the young generations of physicians entering the profession every year, by the public, by research foundations, and by private support of medical research.

Whereas gastrointestinal diseases do not kill many people, they cause distress, pain and suffering in millions of people. The man-hours lost per year makes this aspect a serious economic problem, particularly for the families of affected wage earners. The Statistical Bulletin of the Metropolitan Life Insurance Company in June, 1954, states: "Because of their relatively high frequency as a cause of sickness and disability, ulcers of the stomach and the duodenum rank among the important chronic diseases. According to conservative estimates, approximately half a million people in our country have these conditions in active form. It has been variously estimated that from 5 to 12 per cent of the population will be afflicted with ulcers in the course of a lifetime. In 1953 these disorders accounted for about 9,000 deaths in the United States, or a rate of 5.6 per 100,000 population."

Peptic ulcer is a disease of the young working group of males particularly. If we assume that these patients lose only 2 weeks of working time per year, we can calculate that 7 million working days per year are lost. We believe this estimate is much too low. During 1938, at a steel plant which had an average payroll of 2,125 men, gastrointestinal disease accounted for 2,377 days of lost time, of which 45 per cent was lost due to peptic ulcer. This contrasted with 946 days lost from respiratory disease, and 881 days from cardiovascular disease.

Malignant growths of the digestive organs and peritoneum killed 83,000 people in 1952 in U. S., that is 37 per cent of all cancer deaths. At the present time, most of these cancers cannot be cured except by surgery, and early surgery means early diagnosis. It is at this point where the gastroenterologist comes in; this is his field, and not that of cancer research. If we could use a fraction of the sums given annually for research on the origin and cure of cancer in order to work on early diagnosis, if we could discover new diagnostic tests for early gastrointestinal cancer, we could save a large number of victims.

It is time to stress the importance of gastroenterology. It is time to induce young physicians to specialize in gastroenterology.

It is time to interest the National Funds and Foundations to support gastrointestinal research, both clinical and basic.

It is time to develop a program for specializing in gastroenterology, based on a sound preliminary training in gastrointestinal physiology.

The American College of Gastroenterology is aware of these necessities, and it has, therefore, inaugurated a plan to support gastroenterology as a field of specializing and of research.

We, therefore, announce our plan for:

1. Prizes for work in gastroenterology.
2. Support of basic and clinical gastroenterology by training fellowships.

We are initiating the program this year with Point 1, with funds donated by the Ames Company of Elkhart, Indiana. These prizes will be called the "Ames Awards".

Further details about these awards appear elsewhere in this issue.

Research Committee
American College of Gastroenterology

H. Necheles, M.D., F.A.C.G., *Chairman*
S. S. Berger, M.D., F.A.C.G.
B. J. Ficcarra, M.D., F.A.C.G.
G. B. J. Glass, M.D.
H. G. Rudner, M.D., F.A.C.G.

MARCH 1954 ISSUES NEEDED

All copies of the March, 1954 issue of The American Journal of Gastroenterology (Vol. 21, No. 3) addressed to foreign destinations were lost in the mails.

If you have a copy of this issue which you do not need, please send it to us as our supply is exhausted. In return, we shall be happy to extend your subscription for one issue to compensate for your kindness.

EDITORIAL

Urinary Uropepsin as an Index in Diagnosis of Benign and Malignant States of the Gastrointestinal Tract

The normal range of uropepsin excretion in 24 hours is 1,200 to 3,800 units, with a mean of 2,300 units.

A high level is diagnostic of gastric hypersecretion and is very suggestive of peptic ulcer. Elevated values are also seen in ulcerating cancer, adrenal and pituitary hyperactivity and in patients receiving ACTH or cortisone, or those under stress after surgery, acute myocardial infarction, burns, pain or fractures.

Abnormally low levels, below 1,000 units, are seen in patients with gastric cancer, pernicious anemia, Addison's disease, myxedema, or after gastrectomy.

Excretion of 1,500 units or less with a demonstrable ulcerating gastric lesion is highly indicative of cancer. A low uropepsin determination cannot be used as a sole screening test for gastric cancer, since some patients with gastric cancer have normal excretory values. The test is useful, however, when combined with other screening methods.

Uropepsin excretion appears to be of considerable value in differentiating the site of bleeding in patients with massive gastrointestinal hemorrhage. Patients with cirrhosis or esophageal varices have low values, whereas those with bleeding duodenal ulcers have high values.

The determination is probably preferable to the difficult and often unreliable gastric analysis in evaluation of patients with subtotal gastric resections. The postoperative level of uropepsin is a measure of the amount of functioning gastric mucosa remaining. A value higher than 4,000 units in a symptomatic patient with previous subtotal gastrectomy is suggestive of a marginal or stomal ulcer.

Uropepsin output may be used as an index of adrenal responsiveness, since increases in uropepsin excretion and urinary corticoids are closely related during hormone therapy. The relationship is further emphasized by the exceedingly low levels of uropepsin in patients with Addison's disease or panhypopituitarism and high values with adrenal and pituitary hyperactivity.

The determination may be helpful during steroid therapy, since reactivation or production of a peptic ulcer with hemorrhage or perforation is invariably accompanied by considerable increase in uropepsin excretion.

Vagotomy apparently does not alter uropepsin excretion or response to adrenocortical stimulation.

Acute and chronic stress probably stimulates the stomach and increases uropepsin excretion by a humoral mechanism involving the hypothalmic pituitary-adrenal-gastric axis independent of the vagus nerve or gastric antrum.

SAMUEL WEISS, M.D., F.A.C.G.

BIBLIOGRAPHY

Gray, Seymour J., Ramsey, Colin G. and Reifenstein, Robert W.: Clinical use of the urinary uropepsin determination in medicine and surgery. New England J. Med. **251**:835, 1954.

"THE NEAREST APPROACH TO THE CONTINUOUS INTRAGASTRIC DRIP FOR THE AMBULATORY PATIENT"*

NULACIN

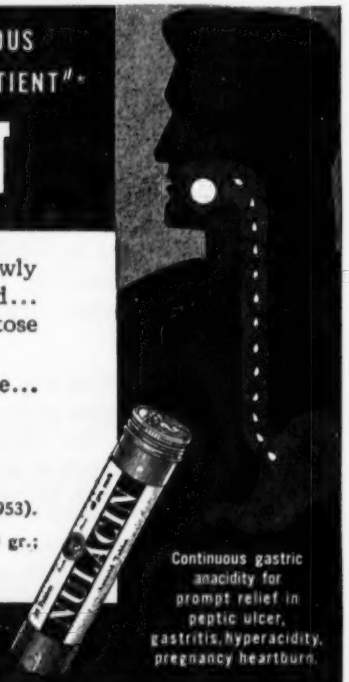
A pleasant-tasting tablet...to be dissolved slowly in the mouth...not to be chewed or swallowed... made from milk combined with dextrins and maltose and four balanced nonsystemic antacids...**

Promptly stops ulcer pain...holds it in abeyance... hastens ulcer healing.

In tubes of 25 at all pharmacies. Physicians are invited to send for reprints and clinical test samples.

*Steigmann, F., and Goldberg, E., J. Lab. & Clin. Med. *42*:955 (1953).

**Mg trisilicate, 3.5 gr.; Ca carbonate, 2.0 gr.; Mg oxide, 2.0 gr.; Mg carbonate, 0.5 gr.



Continuous gastric anacidity for prompt relief in peptic ulcer, gastritis, hyperacidity, pregnancy heartburn.

HORLICKS CORPORATION
Pharmaceutical Division • RACINE, WISCONSIN

Ames Awards Contest of The American College of Gastroenterology

The American College of Gastroenterology, in cooperation with the Ames Company of Elkhart, Indiana, takes pleasure in announcing the establishment of the Ames Awards Contest for the best papers in Gastroenterology.

There will be three classes of awards as follows:

Fellows or Residents in Gastroenterology

First Prize—$250.00, a certificate of merit and a 1 year subscription to THE AMERICAN JOURNAL OF GASTROENTEROLOGY, official publication of the American College of Gastroenterology.

Second Prize—$50.00, a certificate of merit and a 1 year subscription to THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

First or Second Year Internes

First Prize—$250.00, a certificate of merit and a 1 year subscription to THE AMERICAN JOURNAL OF GASTROENTEROLOGY, official publication of the American College of Gastroenterology.

Second Prize—$50.00, a certificate of merit and a 1 year subscription to THE AMERICAN JOURNAL OF GASTROENTEROLOGY.

Best Paper Published

For the best paper published in THE AMERICAN JOURNAL OF GASTROENTEROLOGY, during the twelve months ending 30 June 1955, for which no prize has been previously awarded, $100.00.

Rules and Regulations

All papers submitted must represent original work in Gastroenterology, must not have been previously published except for abstracts or short preliminary reports and must not have been previously presented at any National meetings.

The contents of the papers can be clinical or basic science. Clinical papers must not be case records, but controlled clinical work.

The length of a paper is no criterion for originality or value.

All entries for the 1955 prizes, with the exception of those already published in THE AMERICAN JOURNAL OF GASTROENTEROLOGY, must be typewritten in English, double-spaced on one side of the paper and submitted in six copies.

The winning entries will be selected by the Research Committee of the American College of Gastroenterology and the awards will be made at the Annual Convention Banquet of the College, to be held in Chicago, in October 1955.

All papers selected for awards become the property of the American College of Gastroenterology and the decision of the judges will be final. Should none of the papers submitted meet the standards set by the Committee, the Committee reserves the right to withhold the making of any award.

The recipients of the first prizes will present their paper in person at the Annual Meeting of the College.

All unpublished entries must be received no later than 1 September 1955 and should be addressed to the Research Committee, American College of Gastroenterology, 33 West 60th St., New York 23, N. Y.

NEWS NOTES

Course in the Clinical Pathology and Pathology of Parasitic Diseases

A short intensive course on the laboratory diagnosis and pathology of parasitic infections will be presented August 15-27, 1955 at the Louisiana State University of Medicine in New Orleans.

The course is designed primarily for pathologists and technologists. However, general practitioners, internists, pediatricians, gastroenterologists and physicians engaged in the practice of public health and tropical medicine who are interested in the laboratory diagnosis of parasitic infections are welcome to attend. The instruction and training will be of assistance to pathologists who are preparing for board examinations, to pathologists and physicians who are responsible for the diagnosis of parasitic infections in their laboratories and to technologists engaged in this specialty.

The course will include lectures, extensive demonstrations, films and supervised individual laboratory study. Emphasis will be placed upon the practical aspects of laboratory diagnosis of common parasitic infections, including training in stool examination and stool concentration technics. Abundant material from patients with parasitic diseases endemic in this area will be available for examination. Comprehensive slide sets containing parasitic organisms in tissue sections will be studied. Library facilities are available. The medical school building is air conditioned.

Registrants should bring their microscopes, equipped with mechanical stages, and their microscope lamps. A limited number of places will be available. The fee for the course is $50.00.

Persons interested in attending this course may write to: Dr. Clyde Swartzwelder, Department of Microbiology, Louisiana State University School of Medicine, 1542 Tulane Avenue, New Orleans 12, Louisiana.

Medical Meetings in the Bahamas

With the agreement of the Chief Medical Officer (Bahamas), it is intended to provide facilities for lectures and clinical demonstrations at the New Bahamas General Hospital for doctors who spend their holidays in Nassau. In addition, an auditorium will be available, situated in the beautiful gardens of the British Colonial Hotel next to its own private beach.

Commencing April 1, 1955, arrangements have been made enabling doctors and their families to stay in Nassau at the British Colonial Hotel, one of the most luxurious hotels in the Caribbean, at especially reduced rates.

Eminent medical men from both sides of the Atlantic will be invited as guest speakers. Family doctors from the United States, Canada, Great Britain and other countries will have the opportunity of spending an unforgettable holiday in the company of their colleagues in one of the most beautiful holiday resorts in the world. The climate and recreational facilities of the Bahamas are unsurpassed.

Some of the principal air lines have agreed to offer special arrangements, which together with the generous offer of the management of the British Colonial Hotel will enable doctors and their families to enjoy a unique holiday at exceptionally low cost.

There is a registration fee of $50.00 for each doctor participating in the postgraduate assemblies. There are no other fees.

It is thought that most doctors will like to stay for a period of two weeks, and accordingly group travel arrangements will be available from the beginning of April.

Inquiries for further details may be directed to: Dr. B. L. Frank, 1290 Pine Avenue West, Montreal, Canada.

Publications Editor Sought

The Office of The Surgeon General, Department of Army, is seeking the services of a Chief Publications Editor to assist in the development of the Army Medical Department in World War II.

More specifically, someone is needed with supervisory ability to plan, direct and coordinate editorial and publication activities relating to the approximately twenty-five clinical volumes of the History and in the case of more complex manuscripts to make critical editorial review of such manuscripts to determine such points as literary quality, accuracy of documentation, accuracy of statistics and their interpretation, accuracy of quotations and illustrative materials.

The position to be filled is under U. S. Civil Service and pays a salary of $7040 per annum with $200 increases every seventy-eight weeks up to a top of $8040 per annum.

Interested candidates should write to: The Surgeon General, Department of Army, Washington 25, D. C., ATTN: MEDCM-CP.

President's Message

Governing Boards, medical and otherwise, must be made up of men who, by virtue of age, skill, and aptitude have qualified to minister to the needs of their constituents. Unusual powers and authority are vested in them, with the hope that the membership at large will benefit to the common good. In Medicine, it adds up to a high standard of practice through the use of better, and simplified technics. Narrowing it down to gastroenterology, and its allied specialties, it means a devotion to our College and what it stands for.

Your Executive Committee, and your Board of Trustees are busy at the moment with the details of organization which make for the smooth running of our College. We are well aware of some of our errors in judgment, and administration, and steps are being taken to correct them. I would appreciate well thought out suggestions from our membership. These should be geared to a National scope, but applicable to all levels and communities.

Originality, forethought, and vision will take us far in our chosen field. There must be men in our midst, who have the fire, but as yet have not let the light glow. This is the Forum for the youthful, and enthusiastic, gastroenterologically minded physician.

As of the first of March, there were a number of men who were delinquent in payment of their dues. May I strongly urge those few to send in their checks or, if there is a personal objection or hardship, inform the Executive Secretary. Nothing can be done about a change in the dues before the Annual Meeting of the Trustees. At that time, there will be a reconsideration and probable revision of the present schedule. You will find your Officers ready and willing to cooperate and assist but, especially, interested in increasing the services of the College to you, as far as the budget will permit.

This is your organization, and your responsibility. Let's always be humble, helpful, and worthy.

Lyon A. Ferguson

ABSTRACTS FOR GASTROENTEROLOGISTS

ABSTRACT STAFF

JOSEPH R. VAN DYNE, *Chairman*

ABE ALPER
ARNOLD L. BERGER
A. J. BRENNER
J. EDWARD BROWN
JOHN E. COX
IRVIN DEUTSCH
LEROY B. DUGGAN
KERMIT DWORK
HEINZ B. EISENSTADT
SAMUEL S. FEUERSTEIN
HANS J. JOSEPH
LOUIS K. MORGANSTEIN
JACOB A. RIESE
H. M. ROBINSON
LOUIS A. ROSENBLUM
ARNOLD STANTON
REGINALD B. WEILER

GASTROINTESTINAL TRACT

THE TREATMENT OF ASCARIS LUMBRICOIDES INFECTIONS WITH PIPERAZINE: H. W. Brown. J. Pediat. 45:419 (Oct.), 1954.

Forty-six out of the 51 ascaris-infected children passed all their worms as a result of a five-day treatment with syrup of piperazine citrate (antipar). Children with a weight up to 30 pounds received 2.5 c.c.; with a weight of 31 to 60 pounds, 5 c.c.; and all persons above 61 pounds, 10 c.c. of the drug twice a day. The cure rate was 90 per cent with this dosage. Therapeutic failures may depend on the number and location of the worms, on the presence of certain foods in the gastrointestinal tract, and on different individual absorption rates of the drug. The five-day course of syrup of piperazine is safe and causes little toxicity. The same daily dosage has to be given for a pin worm treatment for 10 to 14 days and has been well tolerated.

H. B. EISENSTADT

MEDICAL AND SURGICAL MANAGEMENT OF DIVERTICULITIS IN GERIATRIC PATIENTS: R. J. Priest, B. E. Brush and L. J. Gregory. J. Am. Geriatric Soc., 3:55-63, (Jan.), 1955.

The incidence of diverticulitis is increasing with the changing age pattern of the population. In uncomplicated diverticulitis in geriatric patients, conservative medical management is recommended, with absolute bed rest and a liquid or low-residue diet during the acute infection. Antibiotics and antispasmodics are used, as is liquid petrolatum if severe constipation or partial obstruction is present. The most important complication during medical management was partial or temporary bowel obstruction, which usually responded to conservative therapy, including intubation and antibiotics. The complications of diverticulitis which required surgical intervention are: free perforation, chronic obstruction, fistula formation, possible malignancy, hemorrhage (in one case) and recurrent stenosing diverticulitis. The operative procedures used are outlined. The one recommended for most geriatric patients with surgical complications of diverticulitis is a three-stage resection of the involved segment of colon.

ARNOLD L. BERGER

GASTROINTESTINAL BLEEDING IN HEREDITARY HEMORRHAGIC TELANGIECTASIS: Gerald A. Williams and Irving B. Brick. A.M.A. Arch. Int. Med., 95:41 (Jan.), 1955.

A 51-year old male patient suffering from intermittent epigastric distress had severe attacks of melena and hematemesis over a period of three years which finally led to a partial gastric resection. However, this operation improved the bleeding only temporarily. The patient had a small telangiectasia on his lip and another one under his tongue and several red nevi over his anterior chest. There was a family history of

similar lesions of the skin and mucous membranes. The patient never revealed any nose bleeding. All hematological examinations were normal except a strongly positive Rumpel Leede tourniquet test. Gastroscopy revealed several bright red small lesions from which blood was oozing. As none of the medications, including corticotropin adrenosen, androgen and estrogen were helpful in curbing the gastrointestinal bleeding, a total gastrectomy was finally performed. Unfortunately, the patient continued to bleed from his small bowels. This case demonstrated the unsatisfactory status of both medical and surgical therapy of this disorder.

H. B. EISENSTADT

STOMACH

PEPTIC ULCER IN THE AGED: P. L. Shallenberger and H. M. Perry. Guthrie Clin. Bull., 23:241 (April), 1954.

The incidence of peptic ulcer in patients over 60 has been reported by various authors as between 10.5 and 22.0 per cent. Approximately 44 per cent of the deaths occurred in this older age group. The authors' series of 143 cases of peptic ulcer in this age group is discussed as to incidence, symptoms, treatment, complications and mortality. In old age, in uncomplicated peptic ulcer, therapy is conservative. Surgery is indicated in the elderly patient when the physical condition is good and there have been numerous recurrences and some of the classic complications; hemorrhage and stenosis being the most frequent in this series. Subtotal gastrectomy is the procedure of choice.

ARNOLD L. BERGER

SUBCOSTOSTERNAL DIAPHRAGMATIC HERNIA: Karl F. Hoffmann and Alexander J. Chilko. Ann. Int. Med. 41:617, (Sept.), 1954.

The definition, symptoms and diagnosis of subcostosternal diaphragmatic hernia are discussed. The common errors in the diagnosis of this condition are emphasized, and a case previously diagnosed as "heart disease" is reported. Indications for surgical treatment are presented. For cases without imperative reasons for surgery, the usually accepted measures are mentioned, and a more active medical regime is proposed for treatment of suitable patients who refuse surgical treatment.

FRANZ J. LUST

ETIOLOGY AND MEDICAL THERAPY OF DIAPHRAGMATIC HERNIAE: P. Hillemand and Y. Barre. Presse Med. 84:1791-1793, 1954.

The ascent of the cardia through the esophageal hiatus presupposes a certain number of isolated or collective disorders as follows:

a) Often a muscular or peritoneal predisposition,

b) A disorder in the tonicity of the pillars (controlled by the sympathetic since the phrenic is a motor nerve) due to a vegetative imbalance, an inflammatory rheumatic area, or a digestion factor. This is to say that endocrine disturbances may play a neurovegetative or a muscular nutritional role.

In general the etiological results were as follows:

Mechanical abdominal compression may be extrinsic.

Intrinsic compression is rare. The role of pregnancy is probably more endocrine than mechanical. Ascites, even of the distended type is rarely at fault.

Rachitic lesions: The following may be observed:

1.—A posttraumatic Kummel-Verneuil type aspect.

2.—An aspect of scoliosis with more or less pronounced angularity.

3.—A definitely inflammatory appearance consisting of "becs", osteophytes, or more posterior lesions of costovertebral joints between D7 and D10 and which may accompany the preceding.

Endocrine disturbances can be classified under three syndromes:

1. *Genital disorders:*—a) In the female, D.H. occurs 5 times out of 8. The menopause, the period at which such disorders

most frequently commence, is ordinarily difficult and prolonged. During the period of genital activity, D.H. may be observed to appear from the age of puberty on, then in women suffering from an early and prolonged "hyperestrinism", and lastly during pregnancy.

b) In the male the genital factor is less important, manifesting itself by functional deficiency either through a lowering of hormone secretion observed in the urine, or, more frequently, through the interference of a spasmophilic or hypothyroid component.

2.—*Spasmophilic conditions*, as is well known, are quite frequent. They play a definite but rarely isolated role in the mechanism of D.H. and treatment of such conditions has often improved digestive disorders.

3.—*Hypothyroidism* has externalized itself in 80 per cent of our cases with a lowering of basal metabolism from 10 to 37 per cent.

4.—*Association* of these groups may give the following: in some cases, the triad made up of gonadotrophin excess, spasmophilia and hypothyroidism—in others, a combination of hypothyroidism and spasmophilia in which the latter element sometimes conceals the clinical aspect to the point of roughly simulating hyperthyroidism.

In conclusion, *the therapeutic side* of the question is interesting. In the case of rachitic disease, they tried dorsal radiotherapy to relieve congestion resulting in functional improvement only of the D.H. but no radiological improvement. They then tried concentric transverse ionization with results which appear encouraging.

The results of endocrine treatment are more definite.—As regards the genitals, before the menopause, progesterone played an adjuvant role. After the menopause, we might stress the fact that only one of all our cases of D.H. responded to estrogens. Pure spasmophilic treatment effected cure in two months of a D.H. in a 20-year old girl. Lastly, by means of the *thyroid treatment*, we are obtaining a high rate of functional improvement and marked or total radiological improvement in roughly half of the cases.

The authors insist, in closing, on the necessity of prolonged treatment or risking a relapse, and to offer the hope that an endocrine-physical therapy combination may set a pattern for medical treatment of D.H.

INTESTINES

THE ROENTGENOLOGICAL APPEARANCE OF THE SMALL INTESTINE IN SPRUE: David Adlersberg, Richard D. Marshak, Henry Colcher, Stanley D. Drachman, A. I. Friedman and Chun-i Wang. Gastroenterology 26:548-578. (April), 1954.

Forty patients with sprue have been studied clinically and roentgenologically over a period of 1-17 years. These patients were observed roentgenologically prior to and following treatment in the hospital, although the vast majority had received some form of antianemic therapy before coming under control of the authors. Three patients revealed a normal small bowel pattern. The remainder exhibited two distinctive patterns. The first and most characteristic was observed in 70 per cent of the patients in this series and consisted of dilatation most prominent in the mid- and distal jejunum, segmentation, seen as large barium-filled loops of ileum best visualized during the evacuation of the barium meal, thickening of the mucosal folds and the presence of hypersecretion. While each of these features might occur in a wide variety of disorders their combination, localization and intensity are more frequent in and much more characteristic of sprue. In the second pattern, segmentation is marked, early and persistent and present throughout the small bowel, secretions are pronounced and dilatation is slight to moderate. This latter pattern occurred in only 10 per cent of the patients in this series. It is also observed on occasion in those conditions and diseases that simulate sprue, namely nephrosis, hyperthyroidism, cirrhosis, pancreatic steatorrhea, pellagra and other deficiency states and therefore, is being referred to as the sprue-like pattern.

Differential diagnosis must also include organic diseases of the small bowel including lymphosarcoma, ileojejunitis, tuberculosis, amyloidosis and scleroderma. Roentgen evidence of improvement in the sprue pattern was significant in two patients following steroid therapy, and in four patients who have been treated for many years with

antianemic therapy. Nevertheless, in most patients there exists a marked discrepancy between the degree of clinical improvement and the roentgen changes reflecting that improvement. The "sprue pattern" is sufficiently distinctive roentgenologically to separate it from the heterogenous group of conditions heretofore labeled with the roentgen diagnosis of "irritation pattern", "enteropathy in deficiency states", "deficiency pattern" or "disordered motor function".

FRANZ J. LUST

MANAGEMENT OF DIABETES BEFORE, DURING, AND AFTER ANORECTAL AND COLON SURGERY: Maurice Protas. Am. J. Proct. 5:222-227 (Sept.), 1954.

The diabetic patient under good control does not present any serious problem for either emergency or elective surgery, and the results and recovery should be as good as in the nondiabetic patient. Good control of the diabetes are insured by proper administration of vitamins, proteins, fluids, electrolytes, carbohydrates and insulin, and result in a good surgical recovery. Spinal anesthesia is the anesthetic of choice for the diabetic requiring colonic surgery, but the anesthetic should be chosen to suit the individual case. A plan is discussed for preoperative, operative, and postoperative management. Successful surgery on diabetics depends upon careful and full cooperation between the gastroenterologist or internist, the anesthetist and the surgeon.

ARNOLD L. BERGER

REFLECTIONS ON REGIONAL ILEITIS, TWENTY YEARS LATER: Burrill B. Crohn and Henry D. Janowitz. J.A.M.A. 156:1221 (Nov.), 1954.

The cumulative experience of the last 20 or more years has justified the classification of regional ileitis as a pathological and clinical entity. The most important expansion of the concept of this disease has been the recognition that granulomatous cicatrizing lesions may be found in all areas of the small intestine. Although the cause of the disease remains unknown, the characteristic pathological process, especially the local lymphatic involvement, has been clearly established. The clinical relationship of regional ileitis or enteritis to chronic ulcerative colitis in the combined form of the disease remains puzzling. In the absence of specific therapy, all currently employed measures, including the use of corticotropin and cortisone are simply supportative. The high rate of recurrences of ileitis following the short-circuiting or the resection type of operation is leading to a re-evaluation of the criteria for operation. The current trend of thinking is to defer operation until the pathological process appears to be quiescent and to restrict surgery to the complications of the disease, namely, obstruction and fistulization.

FRANZ J. LUST

INTESTINAL OBSTRUCTION AND FLUID BALANCE: Frank H. Hodgson. J. Missouri M. A. 52:107, (Feb.), 1955.

The author reviews the important relationship between intestinal obstruction and fluid balance by reviewing the important points in the diagnosis of small intestinal obstruction. More than 70 per cent of small bowel obstructions are caused by bands and herniae. Pathological physiology starts with violent peristalsis followed by paralysis and distention. There is an accumulation of fluids as absorption decreases and bloody fluid passes into the gut and peritoneal cavity as venous congestion and increased capillary permeability ensue. Peritonitis and gangrene follow. The higher the obstruction the worse the vomiting. In lower ileal obstruction fecal vomiting may be present. Pain is cramp-like and periumbilical. The physical findings of distention, peritoneal irritability, and high pitched auscultation signs are present. X-ray evidence of obstruction includes gaseous distention of the intestinal loops with fluid levels. The laboratory studies of urine, blood counts, blood chemistry aid in the diagnosis. The systemic effects of electrolyte loss and its subsequent treatment is gone into in detail by careful study of the patient with intestinal obstruction and an understanding of fluid balance. The mortality rate of this condition can be appreciably lowered.

JACOB A. RIESZ

LIVER AND BILIARY TRACT

HEPATIC TESTS IN METASTATIC CARCINOMA OF THE LIVER: R. L. Simons. Am. J. M. Sc., 17:312-316, (Sept.), 1954.

The necropsy protocols of 73 cases of metastatic carcinoma with and without jaundice, were studied in an attempt to correlate the presence of metastases in the liver with changes in cephalin flocculation, thymol turbidity, alkaline phosphatase, and serum gamma globulin. Approximately one-half of the cases studied had jaundice, and approximately one-half of the jaundice cases had malignant obstruction of the extrahepatic ducts in addition to metastases in the liver.

It was found that cephalin flocculation and thymol turbidiy are not abnormal frequently enough in the nonicteric patient to be of diagnostic significance. When jaundice was due to metastases alone, there was no significant change in the frequency or degree of abnormality of either of these tests. The serum gamma globulin and alkaline phosphatase were frequently elevated in the nonicteric patient with moderate or extensive metastatic involvement of the liver; however neither test reflected to a satisfactory degree early minimal carcinoma metastases to the liver. The authors conclude that malignant obstruction of the extrahepatic ducts with associated metastases to the liver should be considered in the differential diagnosis of the patient with obstructive jaundice of short duration where the hepatic tests indicate obstruction and hepatocellular damage.

J. R. Van Dyne

CORRELATION OF LIVER BIOPSY FINDINGS WITH SURGICAL DISORDERS OF THE UPPER PART OF THE ABDOMEN: R. W. Dunlop, M. B. Dockerty and J. M. Waugh. Surg. Gynec. & Obst., pp. 331-340, (Sept.), 1954.

In a study of 88 patients with normal or nearly normal livers who underwent biopsy of the liver at the time of operation, the following observations were made:

1. Increased fatty metamorphosis was present in 11 per cent of the patients.

2. An increase in the amount of fibrosis, portal space infiltration, and nuclear regenerative and degenerative activity was noted in approximately one half of the patients.

3. The microscopic change did not appear to be significantly related to the type of surgical disorder present except in cases of obstruction of the common duct, in which a high percentage of specimens exhibited partial inflammation.

4. Fibrosis increased with age and with increased duration of symptoms of the disease.

5. Vacuolation of nuclei was present in ¾ of the diabetics and in about ¼ of the nondiabetics.

6. Changes were more prevalent in the biopsy specimens from older persons and in those from women.

J. R. Van Dyne

PRIMARY CARCINOMA OF THE LIVER WITH EARY METASTASIS TO THE SPINE AND INITIAL SYMPTOMS OF PARAPLEGIA: R. D. Trevathan. Am. J. Med., 17:432, (Sept.), 1954.

A 59-year old white male patient became ill with severe pains in the posterior cervical region radiating to both shoulders and arms. This was gradually followed by a complete loss of sensitivity from the level of the second thoracic segment and by a flaccid paresis of the upper extremities with atrophy of the small hand muscles and a spastic paraplegia of the legs. X-ray survey of the skeleton showed a single destructive lesion of the spine at the cervicodorsal junction. Spinal fluid alterations were characteristic of intraspinal block. An exploratory operation revealed an extradural mass identified as a metastasis from an unknown primary carcinoma, the site of which could not be identified during life. Autopsy revealed a malignant cholangioma occupying the uppermost part of the right lobe of the liver. Apart from the solitary bone metastasis extending into the spinal canal no tumor could be found in the body.

H. B. Eisenstadt

HEPATIC COMA: Hugh R. Butt. A.M.A. Arch. Int. Med., 94:331, (Sept.), 1954.

For many centuries hepatic failure has been known to show peculiar nervous and mental reactions prior to the stage of unconsciousness. Only in recent years have biochemical studies been reported showing severe metabolic changes that might give an explanation for this symptomatology. Apparently those are caused by a fundamental disturbance of the enzymes systems. Abnormalities of the blood observed in hepatic coma are metabolic acidosis, low potassium and low magnesium and high ammonia, increased pyruvic acid, ketoglutaric acid and free amino acids especially cystine, methionine and glutamic acid. Furthermore, electroencephalographic changes are present in the form of slowing and disorganization of the alpha rhythm. The spinal fluid shows frequently increased protein, bilirubin and glutamate. The latter substance is thought to be important for the removal of intracellular ammonia which might be responsible for the nervous and mental aberrations.

H. B. EISENSTADT

THE PRESENT OUTLOOK OF EARLY CANCER OF THE LIVER: S. Bonfils, C. Richir and H. Caron. Arch. mal. app. dig., 43:805-818, 1954.

The authors report and analyze 7 observations of early cancer of the liver. The subjects are white males whose ages are between 50 and 70 years.

The essential symptom, often of very early appearance, is abdominal pain which was observed in six cases out of seven. Variable in kind, it gave rise to very different diagnoses: acute pneumopathy, abscess of the liver, appendicitis, subocclusion.

Among other early signs, loss of appetite and icterus should be noted. On the other hand, edema, ascites, digestive hemorrhages, great loss of weight, are habitually late to appear.

Functional hepatic tests are often notably disturbed: serum-albumen (88 per cent) bromsulfalein-phthalein (82 per cent) prothrombin (63 per cent) mac-logan (54 per cent). A white cell count superior to 12,000 is to be observed in 50 per cent of the cases.

Medical literature today confirms these facts and shows that, in Europe, the frequency of early cancer of the liver is far greater than is usually stated. It represents: 2 per cent of global mortality and from 0.5 to 2 per cent of forms of cancer generally. For purposes of associating hepatic cancer and sclerosis, the following points should be emphasized:

1. The two conditions are very generally associated (58 to 100 per cent of cases) and the frequency of their association is on the increase;

2. This association is modified by the clinical or biological signs of the disease. However, in all cases where cancer was not accompanied by a notable hepatomegaly, an important sclerosis of the gland was present;

3. Cases where the appearance of cancer is preceded by a protracted clinical cirrhosis are rare.

The present work is above all clinical and biological. The anatomical documents will be exhibited in a second article.

GUY ALBOT

PANCREAS

EVALUATION OF PROVOCATIVE BLOOD ENZYME TESTS EMPLOYED IN DIAGNOSIS OF PANCREATIC DISEASE: David A. Dreiling and Alexander Richman. A.M.A. Arch. Int. Med., 94:197, (Aug.), 1954.

The diagnosis of pancreatic disease depends mainly on three types of laboratory procedures: 1. the study of the duodenal contents, 2. the study of blood coagulation, 3. the study of blood enzyme levels.

The observation of pancreatic stimulation with duodenal drainage is a valuable but expensive, time consuming and technically difficult procedure. The pancreatic tests based on changes of blood coagulation, i.e., antithrombin titer, are of great interest but require further extensive studies for their evaluation. Therefore, at the present time the most commonly used laboratory procedures are the determinations of blood enzyme levels, i.e., serum amylase and lipase. Unfortunately, these tests are of little value for the diagnosis of chronic pancreatic dis-

orders. In an attempt to overcome this deficiency provocative tests have been suggested determining the blood enzyme level after stimulation of the pancreatic juice with secretin, after increase of the enzyme production by parasympatheticomimetic drugs, i.e., physostigmin, prostigmine, choline and its derivaties, and after blocking of the pancreatic duct system by morphine. These pancreatic secretagogues and sphincterotonic substances were studied singly or in combination in a group of patients as well as normal controls, all drugs were capable of evoking a small transient elevation of blood amylase. These alterations occurred, however, in an unpredictable fashion making it impossible to establish criteria which might enable one to utilize these responses in the diagnosis of pancreatic diseases. Therefore, this investigation leads to the conclusion that provocative enzyme tests are of no practical value in the diagnosis of pancreatic disorder.

H. B. EISENSTADT

DIAPHRAGMATIC HERNIATION OF THE PANCREAS: M. H. Poppel, R. M. Abrams, J. Handelsman and A. Segal, Radiology, 63:91-93, (July), 1954.

This is an interesting report of the position of the pancreas and according to the authors, the first case in which herniation of the diaphragm was roentgenographically demonstrated.

The pancreas is not a relatively fixed viscus but so intimately related to the Vaterian papillary and supra Vaterian regions of the duodenum by the firm insertions of its ducts that displacement of the duodenum will be accompanied by pancreatic displacement.

IRVIN DEUTSCH

METABOLISM

DIAGNOSIS OF ACUTE PORPHYRIA: Eric G. Saint, D. Curnow, R. Paton and John B. Stokes. Internat. Med. Dig., 65:201, (Oct.), 1954.

Three cases of acute atypical porphyria are described, one with evidence of pancreatitis. The latter occurred in a 27-year old female who had a sudden attack of nausea and vomiting with epigastric pain radiating to the back suggesting pancreatitis. This diagnosis was confirmed by the finding of a raised serum amylase level. The urine was dark, suspicious of bile, but careful investigation revealed that the color was due to porphyrins. The Watson and Schwartz test for porphobilinogen was also strongly positive. All liver function tests were normal except a 12 per cent BSP retention at 30 minutes. There was a history of a similar attack six months previously. Various muscle pains on back, neck and legs were present at the time of these attacks. The differentiation of acute porphyria from various abdominal diseases is mainly based on the urinary findings especially the Watson and Schwartz test. The cause of abnormal hepatic and pancreatic function in this disease remains obscure; however some small necrotic lesions in both organs have been found at autopsy.

H. B. EISENSTADT

AUTONOMIC NERVOUS SYSTEM INVOLVEMENT IN DIABETIC NEUROPATHY: Leonard H. Brandon, Jr. Am. J. Med., 17:866, (Dec.), 1954.

Chronic refractory diarrhea can be a symptom of diabetic neuropathy. The diabetes might be mild, not requiring insulin injections, or might be well adjusted, and other neuropathic symptoms may be entirely absent. Fatty diarrhea of external pancreatic insufficiency is rarely present. Other gastrointestinal symptoms of diabetic neuropathy are severe constipation, constipation alternating with diarrhea, gaseous distention, borborygmi and urgency especially shortly after meals. X-ray studies may show disturbed intestinal motility with puddling and scattering of barium. Delayed gastric emptying may also be observed and is usually associated with nausea and sometimes even with vomiting. The treatment remains problematical. Bal had a salutatory effect.

H. B. EISENSTADT

STRESS AND SECRETION IN MAN. I. A STUDY OF THE MECHANISMS INVOLVED IN INSULIN HYPOGLYCEMIA: H. Shay. Am. J. M. Sc., 228:630-642, 1954.

Evidence that stress, ACTH, and cortisone stimulate gastric secretion was presented by Gray and his co-workers. More recently Porter, French and their associates have demonstrated in monkeys that the stress effect of insulin hypoglycemia, acting on the posterior hypothalamus, initiated reactions that resulted in increased gastric secretion and that intact adrenals were necessary for this response to occur. The author's experiments offer support for a similar mechanism in man. Furthermore, the evidence points to the probability that adrenalin is liberated in the stress effect of insulin hypoglycemia and plays an important part in the cycle that results in the stimulation of gastric secretion. It is believed that it will be necessary to consider an adrenal phase of gastric secretion in the peptic ulcer problem and that this phase is a significant part of the harmful somatic mechanisms activated by stress reactions.

J. R. VAN DYNE

PATHOLOGY AND LABORATORY RESEARCH

OXYMETRIC STUDY OF THE PORTAL BLOOD: A. Lemaire, E. Housset, P. Casassus and Ph. See. Presse Med. 62:945-946, (19 June), 1954.

Bancroft, Schweik and Blalock have measured portal oxymetry in animals in order to judge the respective parts played by the portal vein and the hepatic artery in bringing blood to the liver. Schwiegk mentioned in his research in 1932 that the percentage of saturation in oxygen of the portal blood is on an average 60 per cent.

Putting aside the work of Bierman and Coll, 1953, who by transcutaneous puncture took samples of portal blood from patients free of all hepatic disorders and found the same figure of 60 per cent, we do not know of any sample of oxygen taken directly from the portal blood supply of a normal or pathological human being.

The authors set themselves the task of studying the portal blood in order to compare its saturation in oxygen, hematocyte, hemoglobin and globular figure. With patients free from hepatic disorders blood was taken from the portal vein during abdominal operations (e.g. gastric ulcer). In 6 cases there was 60 per cent oxygenation.

In the case of three patients suffering from Cruveilhier-Baumgarten's cirrhosis the authors took blood which can be considered as portal blood from the level of the varicose veins of the abdominal wall and found a percentage of saturation between 65 and 87 per cent, that is on an average 76 per cent in 8 tests. In one of these cases the percentage increased during the development of the cirrhosis and passed from 65 to 87 per cent.

With 5 patients suffering from alcoholic cirrhosis without any special malformation of the umbilical venous system but showing well-developed collateral abdominal circulation, blood taken from the collateral veins showed percentages from 63 to 72.

The writers emphasize that in the case of every patient the peripheric blood taken at the same time as the portal blood gave figures of from 35 to 40 per cent and that at the removal of each sample the hemoglobin, globular volume and the globular figure were the same in the two samples of blood.

They conclude: 1. That the portal blood in a normal person contains more oxygen than the peripheric blood;

2. That the portal blood of cirrhotics has a higher percentage of oxygen than that of a normal person and that the percentage of oxygenation of the portal blood increases during the development of the cirrhosis;

3. They think that this strange phenomenon can be explained by arteriovenous shunts notably in the spleen.

These conclusions are contrary to the notion of portal stasis so currently invoked in cases of cirrhosis of the liver. The manometric measurements which they have carried out confirm on the contrary the existence of portal hypertension.

THE EFFECT OF ORALLY ADMINISTERED FOLINIC ACID IN THE TREATMENT OF TROPICAL SPRUE: Ramon M. Suarez, Sr., Ramon M. Suarez, Jr., Roberto Buso and Juan Sabater. Blood, J. Hematol., 9:489, (May), 1954.

The oral intake of antianemic factors in the treatment of sprue is generally less effective than their parenteral injection, with the exception of folic acid which is almost equally efficient with oral as well as parenteral administration. Five cases of tropical sprue were treated with oral calcium leucovorin to investigate the effect of ingested folinic acid on this disease. In spite of submaximal reticulocyte response all patients had a good clinical and hematological remission. However, this occurred only with a dose of not less than 15 mg. per day, regardless of the presence or absence of free hydrochloric acid in the stomach. This study showed that in spite of the fact that folinic acid appears to be much more active than folic acid in laboratory tests, the latter substance is more efficacious at the same dosage level in the oral treatment of acute tropical sprue than folinic acid.

H. B. EISENSTADT

RESEARCH ON PATHOGENESIS OF SHAY'S ULCER: E. Aron, Charles Nezelof and J. Guesle. Arch. mal. appar. dig., 43:496-504, (May), 1954.

Recalling the work done by the French School, especially that of Debray and Laumonier, and of Lambling, the authors specify that the ulcer of pyloric ligature is not a direct result of gastric distention or peptic digestion.

The pylorus which is a "zone reflexogene" in the rat determines after trauma a neurovascular reaction in the stomach. An increase of capillary permeability determines subepithelial infarctions which communicate with the gastric lumen.

On this experimental basis, the authors demonstrate the protective effect of the vasodilators (nicotinic acid), the aggravating effect of Cortisone and Desoxycorticosterone and the protective effect of the somatotrophic hormone. These hormones exert a direct action, antiphlogistic or prophlogistic, on the gastric wall.

The "ganglio-plegiques" (Pendiomide) do not inhibit the appearance of ulcers, but the derivatives of phenothiazine especially Chlorpromazine exert a total inhibition of the phenomenon. It is shown to be a localized action increasing the resistance to anoxemia and diminishing the vascular permeability.

On the other hand different interventions practiced concomitantly with pyloric ligature (adrenalectomy, unilateral and bilateral nephrectomy, castration) prove to be efficacious in preventing the phenomenon, the percentage of success being extremely variable.

The histological lesions of the liver, adrenals, and kidneys in the rat could be equally interpreted as the effect and not the cause of pyloric traumatism.

The authors do not think that Shay's ulcer could be considered as an experimental ulcer capable of enlightening the pathogenesis of the human ulcer and they doubt the specificity of the numerous means of protection studied at the present time.

GUY ALBOT

BOOK REVIEWS FOR GASTROENTEROLOGISTS

SURGERY OF THE CECUM AND COLON: Stanley Aylett, M.B.E., M.B., B.S., B.Sc., F.R.C.S., Surgeon of the Westminster Hospital Teaching Group, etc. 295 pages, well illustrated. E. & S. Livingston, Ltd., Edinburgh and London—Williams & Wilkins Co., Baltimore, Md., 1954. Price $9.00.

Eighteen well written and illustrated chapters, extensive references and index should appeal to internists as well as surgeons, who will find this monograph a worthwhile addition to their medical literature.

Usually most medical books printed abroad fail to recognize or purposely omit references to American literature dealing with the same subject. Not so with Aylett's Surgery of the Cecum and Colon; here the reader will find no such omission.

In addition to the well printed text, the illustrations, black and color, are outstanding.

The author as well as the publishers are to be congratulated on bringing out this monograph.

1953-1954 YEAR BOOK OF ENDOCRINOLOGY: Edited by Gilbert S. Gordon, M.D., Ph.D., Assistant Professor of Medicine, University of California School of Medicine, etc. 390 pages, illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1954. Price $6.00.

1953-1954 YEAR BOOK OF PATHOLOGY AND CLINICAL PATHOLOGY: Edited by B. Wartman, B.S., M.D., Morrison Professor of Pathology, Northwestern University, etc. 485 pages. The Year Book Publishers, Inc., Chicago, Ill., 1954. Price $6.00.

1954-1955 YEAR BOOK OF MEDICINE: Edited by Paul B. Beeson, M.D., Carl Muschenheim, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., Franz J. Ingelfinger, M.D. and Philip K. Bondy, M.D. 711 pages, illustrated. The Year Book Publishers, Inc., Chicago, Ill., 1954. Price $6.00.

These three books of the Year Book series, as in previous years, need no introduction to the physician. They have become a real necessity in up-to-the-minute practice of general or specialized medicine.

Once the physician sees one of the series of these Year Books, he will find that it is a comprehensive review of the world's best medical literature and will greatly aid him in making a better diagnosis and institute treatment in general medicine, surgery, or the specialties.

These Year Book volumes are highly recommended.

AMEBIASIS: Ernest Carroll Faust, A.B., M.A., Ph.D., Professor of Tropical Diseases and Hygiene, Tulane University of Louisiana, New Orleans, La. 154 pages, illustrated. Charles C. Thomas, Springfield, Ill., 1954. Price $4.75.

This well written and timely monograph on amebiasis, divided into six chapters, should be interesting reading for the student and the physician who is intent on diagnosing, treating and eradicating this public health scourge.

The author discusses the geographic distribution and human susceptibility to infection in a lucid manner and also calls attention to the susceptibility of Americans and Europeans who readily acquire acute amebic dysentery while visiting Panama, the low lands of Mexico and Central America, coastal Columbia, Venezuela, the Guianas, northern Brazil, Morocco, Egypt, India, Indo-China and the Philippines.

The chapter dealing with manifestations and clinical evidences of amebiasis discusses the incubation period, the various manifestations and involvements of the liver and the viscera, the pleura and lung, the brain and the skin.

In chapter five, the author outlines diagnosis, treatment and the prognosis of amebiasis. A colored insert between pages 80 and 81, illustrates the cysts of the common protozoa of a man as seen in fresh fecal films stained with D'Antonis iodine.

According to Faust, the most valuable amebicides in intestinal amebiasis belong to three groups: 1) iodohydroxyquinolines, 2) arsenic acid derivatives, 3) certain antibiotics.

Under group one belong chiniofon, diodo-

quin and vioform and emetin bismuth iodide. In group two, we have acetarsone, carbarsone and milibis. The latter has recently been found a very valuable antiamebic drug. It is of low toxicity but should be prescribed with caution to patients who have arsenic idiosyncracy.

Certain antibiotics, such as penicillin and streptomycin have no direct action on the ameba.

Antibiotics which are active against amebic infestation are aureomycin and terramycin. The dose of the former: 2 x 0.25 gm. capsules taken orally four times daily for 10 days, while terramycin is given 0.25 gm. capsule orally four times daily for 10 days. Bacitracin and fumagillin are also antiamebic drugs and may be given a fair trial.

Sulfa drugs, chloranephenical, emebin may be found valuable, especially in hepatic and cutaneous manifestations.

Chapter six deals with the control of amebiasis and should be read carefully by the student and the physician.

This monograph is highly recommended as an addition to the busy physician's library.

TEXTBOOK OF ROENTGENOLOGICAL DIFFERENTIAL DIAGNOSTIC. DISEASES OF THE ABDOMINAL ORGANS. (Vol. 2): (Lehrbuch der Roentgenologischen Differentialdiagnostik. Band 2. Erkrankungen der Bauch Organe): Werner Teschendorf. 1,037 pages, 1,610 illustrations. Third enlarged and improved edition. Georg Thieme Verlag, Stuttgart, 1954. Price $44.30.

We want to congratulate Teschendorf on the third edition of his book on roentgenology, for it is an outstanding work. Just to mention one fact, whereas the first edition contained some 900 illustrations, the third edition contains over 1,600 illustrations of the highest quality. Thieme has produced a book which will be one of the basic works in the roentgenology of the abdomen. The clearness of reproduction and text can hardly be surpassed. We have only praise for Teschendorf's book, which is known to many. The entire armamentum of roentgenology is used for demonstrating pathological processes. There are many pages and innumerable illustrations on mucosal studies. Spot films of all parts of the alimentary tract are used. The quality of the illustrations is on such an even level that it seems that all the films were taken during the last year. The new advances of gallbladder and intravenous cholangiography are discussed as Teschendorf is among the first in pioneering in this new road in roentgenology. The author is no stranger to American physicians. Some of his latest studies in this field have been published in the pages of this journal. The text, too, has been supplemented since the second edition by several hundred pages. The book is written in German, but the illustrations are so perfect, that it can be easily used as an atlas, even if one is not fully acquainted with the language. Besides the gastrointestinal tract, the liver, spleen and kidneys are discussed.

Among the very important parts of the book is a section on the operated stomach. This field has not been well presented in other publications, therefore, it will be appreciated by everyone. Many films show the misleading interpretation of films, for instance, due to artifacts, and the correct interpretation is given. A section on small intestinal pathology is especially exhaustive. The index of the book is very complete, comprising 57 pages. The literature concerning every topic is at the bottom of every page.

We recommend the book to all those interested in roentgenology, gastroenterology, surgery and internal medicine. There is an extensive bibliography at the bottom of every page, which covers the American literature to a large extent.

PRACTICAL MANAGEMENT OF DISORDERS OF THE LIVER, PANCREAS AND BILIARY TRACT: John Russell Twiss, M.D. and Elliot Oppenheim, M.D. 653 pages, 136 illustrations, 7 plates, 3 in color. Lea and Febiger, Philadelphia, 1955. Price $15.00.

We wish to congratulate Twiss and Oppenheim on the publication of their book. This is an exceedingly practical publication, based upon the vast personal experience of the authors in this field, where their names have been well known for many years. The work was begun by the late R. Franklin Carter at the former Post Grad-

uate Hospital in New York City (now: University Hospital), where the Medical and Surgical Biliary Tract Clinic has been known for its outstanding work for 25 years.

Diagnostic procedures, such as duodenal drainage, are dealt with thoroughly, with illustrations of microscopic findings which should be useful to those doing this work. Cholangiography is described in its many important aspects including the procedure of Twiss and his associates for visualization of the bile ducts after cholecystectomy by oral administration of dye.

Among the many highly interesting chapters we want to mention are those on the postcholecystectomy syndrome, pathology of the bile ducts, the critical evaluation of liver function tests and the typhoid carrier state. Cirrhosis of the liver is an outstanding chapter.

The section on disorders of the pancreas has been written by William V. Berger. The roentgenological part has been contributed by Samuel L. Beranbaum. The estimation of hepatic function is written by Maurice Bruger, needle biopsy by Alexander S. Honig and parasitic diseases by Brady and Wright. Their contributions are valuable and fit into this book.

This publication is written by medical men, a fact which is of the greatest importance, for this field is too frequently regarded as a field solely for surgery. Medical, not surgical, treatment is described extensively. We consider this book by two outstanding medical men of the greatest value. Diets are thoroughly discussed and explained. Though the material is based on extensive, personal experience, Twiss and Oppenheim have quoted over 3,000 articles in the bibliography, which is appended to each chapter. Every topic is discussed in a short and precise way, which will be extremely valuable to all busy physicians. The index is exhaustive.

There is a new feature in this book: the last chapter, which the authors call an appendix, is devoted to certain technical procedures, not generally available, which are required to make a diagnosis in this difficult field of medicine. Our laboratory technicians will welcome this part, for it gives a description of different methods, and is aided by references in each field.

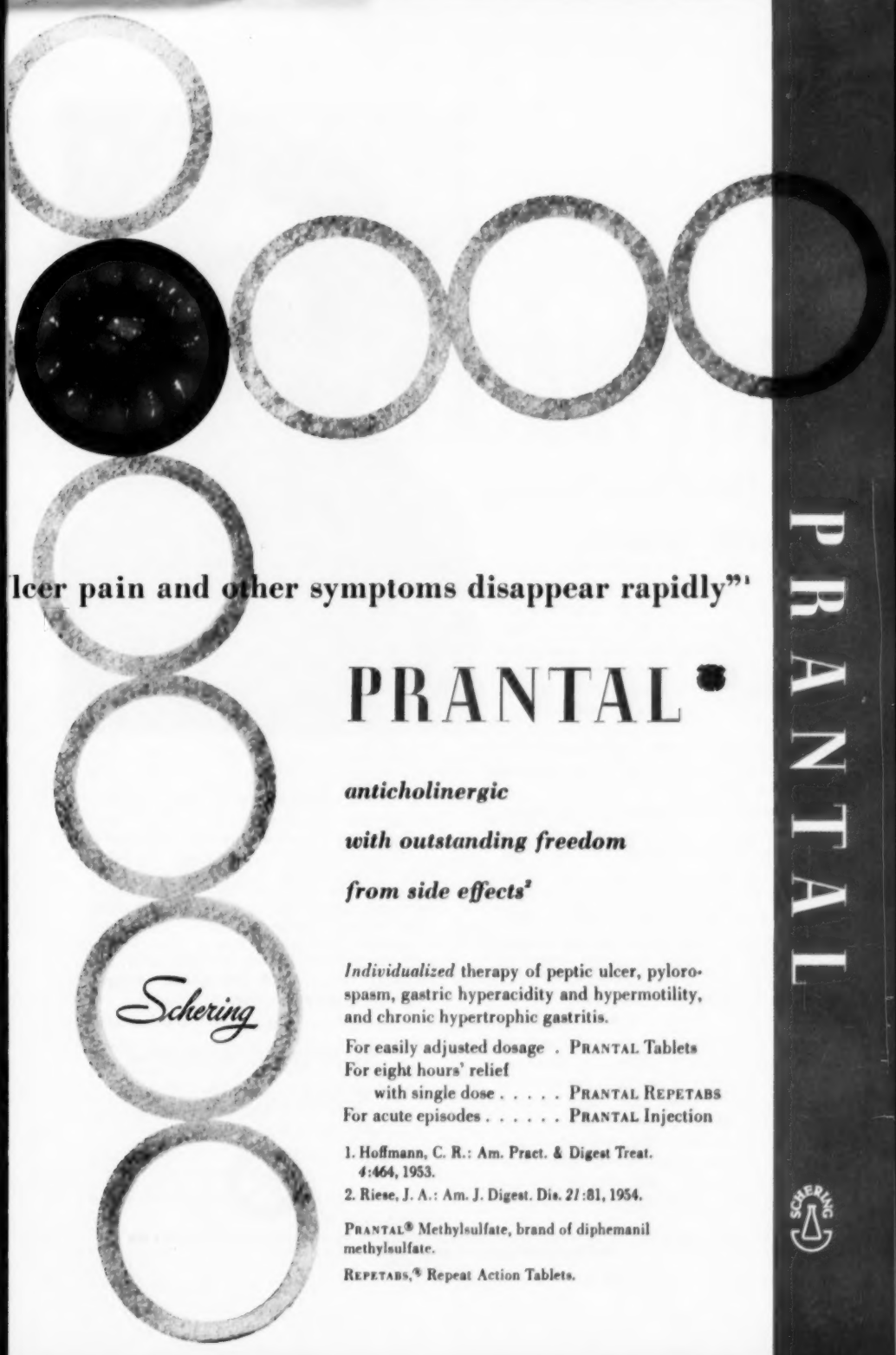
The text is clear and concise. Lea and Febiger have done a good job with the 136 illustrations and plates, some in color. The book will be widely read by all those interested in this field: medical men, surgeons and students alike.

OPERATIVE CHOLANGIOGRAPHY. TECHNIC, DIAGNOSTIC, PRAXIS: Priv. Doz. Dr. Walter Hess. Preface by Prof. Dr. R. Nissen. 201 pages, 150 illustrations. Georg Thieme Verlag, Stuttgart 1955. Price $10.00.

"Operative Cholangiography" is based on the findings of the Department of Surgery in Basle. Hess describes the procedure of cholangiography as it is commonly used and its refinement in connection with manometry. This method was described by Carnot, Caroli, P. Mallet-Guy and Guy Albot. They have all published extensively on this subject. The first part of the book contains a thorough description of this method, which has been worked up and developed in France. In the U.S.A. Roy Upham reported on these methods in 1954. The author presents further, the method of L. Leger for filling of the duct of Wirsung (pancreatography).

Hess' tremendous material is corroborated by surgical findings, which are of the utmost value. The second and third parts of the book deal with the diagnosis and surgery of the bile ducts under cholangiographic control. The author gives a thorough description of biliopancreatic reflux and the roentgenological changes of the pancreatic ducts. Special chapters deal with chronic pancreatitis in gallbladder surgery and with tumors of the bile ducts and the pancreas. The combined methods of manometry and cholangiography are apparently able to unravel many problems in this field.

The book is well written in German. It is so important that we hope it will be translated into English. The illustrations are clear. Each one is accompanied by a drawing, so that fine details can be noticed by the reader. Besides, the history of diseases is added, so that the illustrations are extremely instructive. Rudolph Nissen, the director of the Surgical University Clinic in Basle has written a very interesting introduction. Thieme has done a very good job in the publishing of this book. We recommend it most highly to the gastroenterologist, the surgeon, the roentgenologist and to all those interested in this very important field.



lcer pain and other symptoms disappear rapidly"[1]

PRANTAL®

anticholinergic

with outstanding freedom

from side effects[2]

Individualized therapy of peptic ulcer, pylorospasm, gastric hyperacidity and hypermotility, and chronic hypertrophic gastritis.

For easily adjusted dosage . PRANTAL Tablets
For eight hours' relief
with single dose . . . . . PRANTAL REPETABS
For acute episodes . . . . . PRANTAL Injection

1. Hoffmann, C. R.: Am. Pract. & Digest Treat. *4*:464, 1953.
2. Riese, J. A.: Am. J. Digest. Dis. *21*:81, 1954.

PRANTAL® Methylsulfate, brand of diphemanil methylsulfate.

REPETABS,® Repeat Action Tablets.

Schering

PRANTAL

SCHERING

"The Devil was having wife trouble"

"HERE I AM, twenty-four years old and what have I done?" he had once written. But he was 53, and his face, like his indomitable will, had become seared and toughened by years of Arctic struggle before he reached his ultimate goal.

On December 15, 1909, Robert E. Peary, standing where no man had set foot before, planted the American flag on the North Pole.

His return to his base was so uneventful one of his Eskimos said the Devil must have been asleep or having trouble with his wife.

Actually, good luck of this sort was a rarity to Peary. He had failed six times before to reach the Pole, but he never gave up. He lived all his life by his motto: *I shall find a way or make one.*

Peary's was a motto Americans find easy to understand. In fact, it typifies the practical "strike-out-for-yourself" spirit of the 160 million American citizens who stand behind United States Series E Savings Bonds. Perhaps that's why these Bonds are among the finest investments in the world today. For your personal security—and your country's—why not invest in them regularly!

It's actually easy to save money—when you buy United States Series E Savings Bonds through the automatic Payroll Savings Plan where you work! You just sign an application at your pay office; after that your saving is done for you. And the Bonds you receive will pay you interest at the rate of 3% per year, compounded semiannually, for as long as 19 years and 8 months if you wish! Sign up today! Or, if you're self-employed, invest in Bonds regularly where you bank. There's no surer place to put your money, for United States Savings Bonds are as safe as America!

Safe as America — U.S. Savings Bonds

The U.S. Government does not pay for this advertisement. It is donated by this publication in cooperation with the Advertising Council and the Magazine Publishers of America.

For nausea, vomiting

and gastritis

new

probutylin

(PROCAINE ISOBUTYRATE, RORER)

Probutylin, on oral administration, is an active surface anesthetic to the lining of the upper gastrointestinal tract. Its rapid, direct action is effective in the management of nausea, vomiting and gastritis—also the control of pylorospasm and spasm of the small bowel.

In one series of 104 patients suffering from nausea and vomiting, singultus or pylorospasm, Probutylin gave complete relief to 80%, and the remainder of the patients obtained partial relief.

Exhaustive clinical investigation during the past four years has shown that Probutylin has a low index of toxicity. Patients under medication for more than two years have experienced no untoward effects. The sole contraindication is in certain cases of hypertension.

Recommended dosage schedule

Gastritis: 1 or 2 capsules 20 minutes before meals and antacid (Maalox®) 20 minutes after meals.

Post-alcoholic gastritis: 2 capsules with antacid (Maalox®).

Pylorospasm: 2 teaspoonfuls elixir 5 to 10 minutes before meals.

Nausea and vomiting of pregnancy: 1 or 2 capsules before rising, 4 during day if needed.

Administer Probutylin with as little water as possible. Dilution reduces its effectiveness.

Supplied: Capsules Probutylin, 300 mg., in bottles of 50.
Elixir Probutylin, 10%, in bottles of 180 cc.

Literature and samples forwarded on request.

RORER

WILLIAM H. RORER, INC.

PHILADELPHIA 6 PA.

Now you can do more for

Stress SF Fortified

The availability of such anti-infectives as Terramycin, Tetracyn and penicillin has not altered the wise admonition to "treat the patient as well as the disease." As the National Research Council[1] has emphasized, certain water-soluble vitamins (B-complex and C) and vitamin K are involved in body defense mechanisms as well as in tissue repair and are required in increased amounts during the stress of febrile infections. Yet there is often a considerable reduction in the normal supply of these important nutritional elements in acutely ill patients who are candidates for antibiotic therapy.

Unique new Stress Fortified Terramycin-SF, Tetracyn-SF and Pen-SF contain the stress vitamin formula recommended by the National Research Council[1] for therapeutic use during sickness or injury as a significant contribution to rapid recovery and convalescence. The patient is assured the maximum benefits of modern antibiotic therapy plus the needed vitamin support — without additional prescriptions, and at little additional cost.

1. Pollack, H., and Halpern, S. L.: Therapeutic Nutrition, Prepared with Collaboration of the Committee on Therapeutic Nutrition, Food and Nutrition Board, National Research Council, Baltimore, Waverly Press, 1952.

the patient with infection...

not only fight the infection,

but also Stress Fortify the patient

with a *single* prescription of

®Terramycin-SF

Brand of oxytetracycline with vitamins

CAPSULES (250 mg.)

®Tetracyn-SF

Brand of tetracycline with vitamins

CAPSULES (250 mg.) ORAL SUSPENSION (fruit flavored)
(125 mg. per 5 cc. teaspoonful)

Pen-SF*

CAPSULES (200,000 units)

Brand of penicillin G potassium with vitamins

The minimum daily dose of each antibiotic
(1 Gm. of Terramycin or Tetracyn,
or 600,000 units of penicillin)
Stress Fortifies the patient
with the stress vitamin formula
as recommended by
the National Research Council...

Ascorbic acid, U.S.P.	300 mg.
Thiamine mononitrate	10 mg.
Riboflavin	10 mg.
Niacinamide	100 mg.
Pyridoxine hydrochloride	2 mg.
Calcium pantothenate	20 mg.
Vitamin B_{12} activity	4 mcg.
Folic acid	1.5 mg.
Menadione (vitamin K analog)	2 mg.

for little more than the cost of antibiotic therapy alone

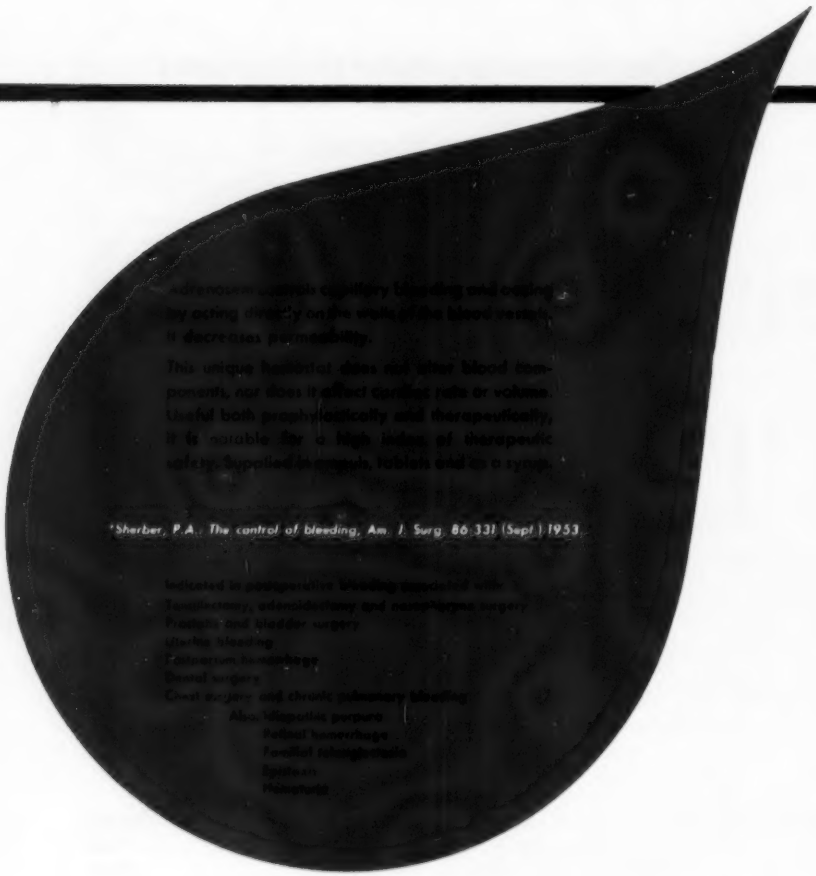
available only from **Pfizer**

PFIZER LABORATORIES, Brooklyn 6, N. Y.
Division, Chas. Pfizer & Co., Inc.

*TRADEMARK

"...a potent antihemorrhagic factor"*

in use in more than 2500 hospitals



*Sherber, P.A.: The control of bleeding, Am. J. Surg. 86:331 (Sept.) 1953

The unique systemic hemostat

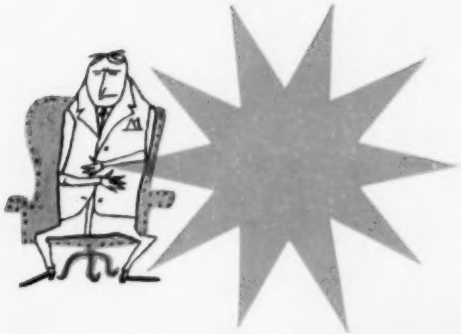
Send for detailed literature

adrenosem®

SALICYLATE

(BRAND OF CARBAZOCHROME SALICYLATE)

THE S. E. MASSENGILL COMPANY, Bristol, Tennessee



a new topical anesthetic for oral administration

XYLOCAINE® VISCOUS ASTRA

(Brand of lidocaine*)

the most effective anesthetic

for the proximal parts of the digestive tract

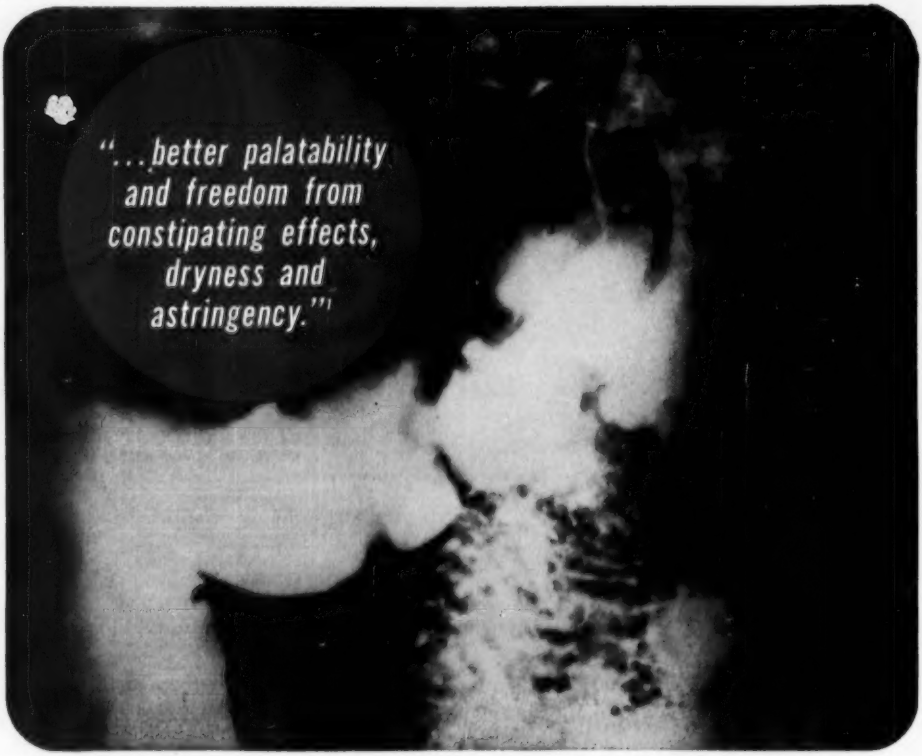
- Quick acting with prolonged effect
- High viscosity and low surface tension permit the anesthetic, Xylocaine Hydrochloride, to come into immediate and intimate contact with the mucous membranes
- Safe . . . nonirritating . . . nonsensitizing.
- Cherry flavored . . . pleasant and easy to take.
- Xylocaine Viscous has proved valuable in the "dumping" syndrome, hiccup, pyloric spasm caused by peptic ulcer, stomatitis, pharyngitis, esophagitis, acute cardiospasm, pylorospasm in infants, severe vomiting of pregnancy, esophagoscopy, gastroscopy, gastric intubation and gastric lavage.
- Contains 2% Xylocaine Hydrochloride in an aqueous solution adjusted to a suitable consistency with carboxymethylcellulose. Cherry flavored for palatability.

Supplied: In bottles of 100 and 450 cc.
Average Dosage: One tablespoonful, administered orally.
Additional information available upon request

ASTRA

Astra Pharmaceutical Products, Inc., Worcester 6, Mass., U.S.A.

*U.S. Patent No. 2,441,498



Morrison, in treating a large series of patients with Maalox-Rorer, describes this better-tolerated preparation as "... a palatable, antacid, demulcent, nonconstipating colloidal suspension of magnesium and aluminum hydroxides, useful for the relief of hyperacidity."

This clinician concludes: "Magnesium aluminum hydroxide gel is more palatable than aluminum hydroxide gel and better suited to the prolonged administration required for the antacid therapy of peptic ulcer and hyperchlorhydria."[1]

A well-balanced suspension, notable for its smooth texture and pleasant flavor, Maalox has gained remarkable patient acceptance.

Supplied: in 355 cc. (12 fluid ounce) bottles. In tablet form, bottles of 100. Each tablet equivalent to 1 fluidram of the suspension.

Samples sent promptly on request.

maalox®

controls hyperacidity

1. Morrison, Samuel: Magnesium aluminum hydroxide gel in the antacid therapy of peptic ulcer, Am. J. of Gastroenterology 22:309 (Oct.) 1954.

WILLIAM H. RORER, INC.
Philadelphia 6, Pa.

Konsyl...

. . . overcomes constipation by the addition of concentrated hemicelluloses

Konsyl is a vegetable concentrate of naturally-occurring hemicelluloses derived from blond psyllium seed. Its use replaces or augments that portion of the diet which supplies the moist, smooth bulk essential to normal peristalsis and easy evacuation.

Konsyl provides hemicelluloses in *concentrated* form — the type of hemicelluloses which you prescribe when you place a patient on a diet high in leafy vegetables, root vegetables, the legumes and fruits. There is one important difference, however. Konsyl is virtually free from the irritating lignin and cellulose found in high residue diets.

HEMICELLULOSES ADD BULK — RETAIN WATER

Hemicelluloses are complex carbohydrates which, with lignin and cellulose, occur in the structural portion of plant tissues. These materials form the non-digestible residue in the normal diet and, in combination, are commonly designated as roughage. The hemicelluloses differ from lignin and cellulose by being less complex chemically.

The hard, woody portions of plants are very high in lignin and cellulose content. It is these portions which form the coarse, harsh part of roughage which causes irritation. The hemicelluloses, on the other hand, are the portion of the residue which absorbs and holds water despite the absorptive powers of the lower colon. By virtue of their water-retaining power hemicelluloses supply only bland, non-irritating bulk. Williams and Olmstead have clearly demonstrated that, of these components of roughage, the *natural* laxative effect is primarily due to the hemicelluloses.

PRESCRIBE KONSYL FOR PATIENTS WHO WON'T FOLLOW DIET

Since patients typically will not follow a prescribed diet, Konsyl is used to supply the hemicellulose they need in concentrated easy-to-take and inexpensive form. Your patient has only to take Konsyl at regular intervals to insure an adequate intake of proper bulk and, consequently, normal bowel habits. Konsyl has no caloric value.

Send for Samples

KONSYL

Available: 6 and 12-ounce cans.

Formula:

Konsyl contains 100% Plantago ovata coating (naturally occurring hemicelluloses)

BURTON, PARSONS & COMPANY

Washington 9, D. C.

Gastric Hyperacidity: etiology

People being people, environmental factors contributory to gastric hyperacidity are hard to remove, even when their role is clearly defined. But, the physician has a sure, simple—even pleasant—way of relieving the acid distress caused by:

- dietary indiscretion
- nervous tension
- emotional stress
- food intolerances
- excessive smoking
- alcoholic beverages

Gelusil promptly and effectively controls the excessive gastric acidity of "heartburn" and chronic indigestion. And it affords equally rapid relief in peptic ulcer. Sustained action is assured by combining magnesium trisilicate with the specially prepared aluminum hydroxide gel.

Free from constipation: Gelusil's aluminum hydroxide component is specially prepared: the concentration of aluminum ions is accordingly low; hence the formation of astringent—and constipating—aluminum chloride is minimal.

Free from acid rebound: Unlike soluble alkalies, Gelusil does not over-neutralize or alkalinize. It maintains the gastric pH in a mildly acid range—that of maximum physiologic functioning.

Dosage—2 tablets or 2 teaspoonfuls two hours after eating or when symptoms are pronounced. Each tablet or teaspoonful provides: 7½ gr. magnesium trisilicate and 4 gr. aluminum hydroxide gel.

Available—Gelusil Tablets in packages of 50, 100, 1000 and 5000. Gelusil Liquid in bottles of 6 and 12 fluidounces.

Gelusil®

Antacid • Adsorbent

WARNER-CHILCOTT